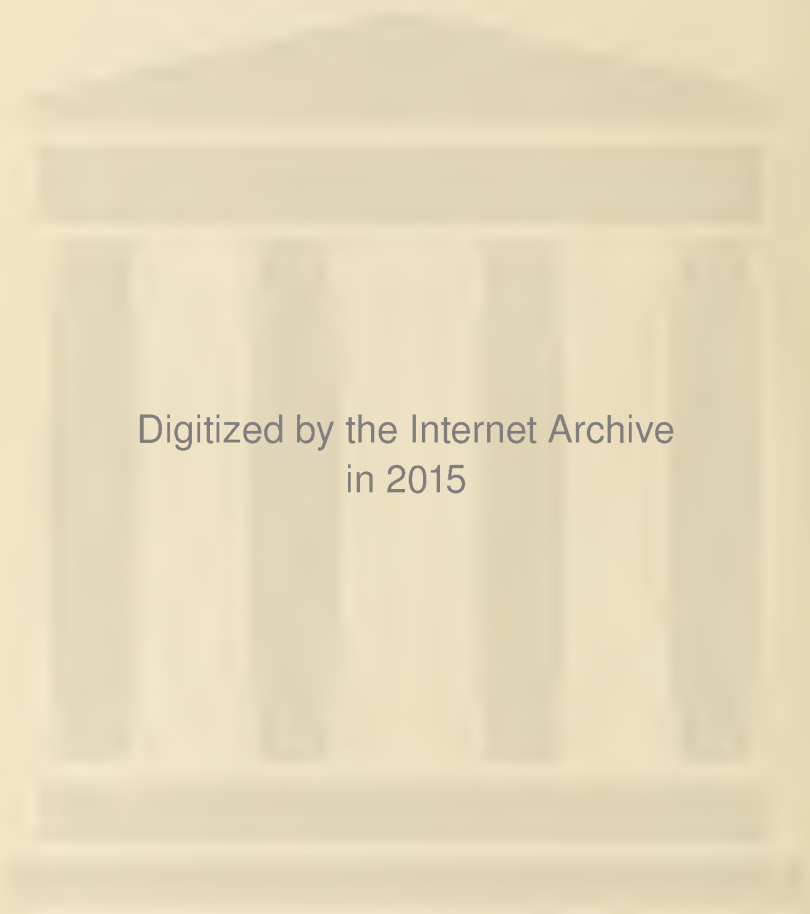






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VOLUME XV  
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## A CLINICAL REVIEW OF DIVERTICULITIS OF THE COLON

REPORT of 108 CASES<sup>1</sup>A. M. SABETI, M. D.<sup>2</sup>

The literature on the subject of diverticulitis of the colon is considerable, but its pathogenesis and treatment has been subject to a great deal of controversy and confusion. Descriptions given in most text books of this subject are incomplete; and the incidence of this disease is sufficiently great as to justify a clinical review of the subject.

This communication is based upon the study of 108 cases of diverticulitis of the colon, admitted to the ward services of the Mount Sinai Hospital, New York during the twelve year period from 1932 to 1945.

Littre (1) in 1700 mentioned the term "diverticular hernia" but without explaining the nature of this condition. Multiple colon diverticula were first described by Cruveilhier (2) in 1849. In 1853 Virchow (3) pointed out the frequent occurrence of diverticulitis as "isolated circumscribed adhesive peritonitis" particularly in the hepatic, the splenic and the sigmoidal flexures of the colon. He attributed the origin of such local inflammatory changes to constipation.

The clinical significance of colon diverticulitis was first recognized in 1898, when Graesser (4) reported a case of diverticulitis of the colon in which the perforation of several chronically inflamed diverticula led to peri-sigmoiditis and stenosis of the bowel. The clinical diagnosis of diverticulosis remained difficult and uncertain until the establishment of modern roentgen-ray diagnosis. DeQuervain (5) in 1914 was the first to demonstrate sigmoidal diverticula by means of x-ray examination, following introduction into the colon of contrast material. Shortly after, the subject was extensively studied by Fischer (6), Beer (7), Mayo (8), Spriggs and Marxer (9), Case (10) and many other investigators.

The term diverticulosis as proposed independently by DeQuervain (5), Spriggs and Marxer (9), and Case (10) in 1914 refers to the presence of uncomplicated, noninflammatory diverticula. Inflammation of the diverticula sufficient to give rise to clinical symptoms is termed "diverticulitis." Inflammation of the structures surrounding the diverticula is called "peridiverticulitis."

Spriggs and Marxer (9) described a "pre-diverticular state" by which they refer to a pathological condition of the colon recognized by x-ray and in which precursors of diverticula may be recognized.

*The incidence of colonic diverticula.* Ochsner (11) reports that seven per cent of 2,984 patients examined roentgenologically after they had received a barium

<sup>1</sup> From the medical and Surgical Services of The Mount Sinai Hospital, New York.

<sup>2</sup> Thesis approved by the faculty of the Graduate School of Medicine of the University of Pennsylvania toward requirements for the degree of Master of Medical Science for graduate work in surgery.

enema were discovered to have diverticulosis. Spriggs and Marxer (9) report that in 1,000 consecutive radiological examinations of the alimentary canal, diverticulosis of the large intestine was recognized in 100 patients. Hayden (12) reports that at the Massachusetts General Hospital, in 6,426 consecutive barium enema examinations, diverticula were found in three per cent of the cases. Forbes (13) stated that approximately one per cent of the general population is afflicted with diverticulosis of the colon.

*Anatomy of the colonic diverticula.* Diverticula are pouch-like protrusions or herniations of the mucosa and submucosa through the interstices in the muscle-coat. Diverticula are classified as congenital and acquired. Congenital or true diverticula of which Meckel's diverticulum is an example, are rare. Their distinguishing characteristic is that the wall of the sac contains all the normal coats of the bowel from which the diverticulum originates. False or acquired diverticula are of much more common occurrence (7), and their distinguishing characteristic is that the pouch is made up of mucosa and serosa. The muscular layers are absent. Gant (14) has stated that it is sometimes possible that the so-called false sac possesses all the bowel tunics instead of being formed by protrusion of mucous membrane through the muscular coat. The congenital diverticula are usually found in the small intestine, while the acquired diverticula ordinarily involves the cecum, colon and sigmoidal flexure, the latter situation being the most common. Diverticula of the large intestine are commonly small and multiple, different in both these respects from the usual form found in the small intestine. In the large bowel, the diverticula develop without any regularity. They are found going into the mesentery or attached to some other part of the intestine. Very often they develop in the haustra alongside one of the longitudinal muscular bands and frequently they grow into appendices epiploicae (7).

*Etiology of the colonic diverticula.* The etiology of the colonic diverticula is not known. There are several theories concerning the formation of the acquired diverticula, all of which probably combine to cause this condition.

1. Obesity; the presence of much fatty tissue in the intestinal walls and the appendices epiploicae has been shown to be the predisposing factor to the formation of diverticula (8, 15, 16).

2. The physiological role of the sigmoidal flexure; the longest retention of fecal material occurs in this portion of the bowel and here, consequently, the pressure from within and the exposure to bacterial damage are liable to be greatest.

3. Pressure from within the bowel; this may be due to the accumulation of the feces, gas or both (9, 14).

4. The relation of the diverticula to the point of entry of the vessels through the intestinal wall; the point of entry of the blood-vessels through the intestinal wall is an area of weak resistance, due to the fact that the vessels are accompanied by a certain amount of lax connective tissue through which an out-pushing of the mucous membrane can more easily take place. This fact was first pointed out by Klebs (15) in the case of acquired diverticula of the small intestine and has been confirmed by Fischer (6) with regard to the large bowel; but the latter view was debated later by the experiments of Beer (7).

5. The variations in size of the vessels; Graesser advanced the theory that chronic congestion of the bowel might be the etiological factor for the formation of the diverticula. This view was confirmed by Wigand (17) but has been debated by Beer (7).

6. Muscular deficiency of the intestinal wall; Beer (7) believes that in view of the often observed fact that the diverticula occur in old people with poor and atonic intestinal muscles (as evidenced by constipation) and are associated with obesity (or obesity followed by cachexia), that this muscular weakness might be the cause of formation of the false diverticula.

7. Infectious origin; of one-hundred patients with diverticula studied by Spriggs and Marxer (9), sixty-five were subjects of the small abscesses or septic granulomata of the teeth.

Thus, it seems that probably no one factor is sufficient in itself to bring about the colonic diverticula. Constipation is extremely common, while diverticulosis is comparatively rare. Venous congestion is also common and the combination of this with constipation is frequent. Thus, it would seem that in addition to constipation and venous congestion, which are predisposing factors, there needs to be an acquired or congenital muscular weakness and a defect in arrangement of the connective tissue to cause the formation of the colonic diverticula (7, 18).

*Pathology of diverticulitis of the colon.* Diverticula in themselves are innocuous as long as their structure remain unchanged. On the other hand, due to varying conditions of intrainstestinal pressure a varying amount of atrophy, particularly of the mucosa, may take place with a hypertrophy of the submucosa and the serosa. If fecal material is constantly passed into a false diverticulum, the material tends to remain imprisoned, especially when the neck of the sac is narrow. The feces become inspissated and form a fecalith, the constant pressure of which abrades and ulcerates the mucosa leading to acute or chronic diverticulitis.

The sequence of events and complications of diverticulitis depend upon the nature, site and extent of the pathologic process. There may be a thinning of the mucosa with the passage of toxins into the bowel wall with resultant local peritonitis and adhesions. The diverticulum may become strangulated and slough off into the peritoneal cavity. An abscess may form which may remain localized or perforate, presenting symptoms similar to the perforation of any intra-abdominal abscess into the bowel or free peritoneal cavity.

The general picture is that of a peridiverticulitis and local peritonitis with secondary adhesions forming between the colon, the dome of the bladder, and the surrounding omentum and intestine. As the inflammatory process progresses, a local abscess develops. Whether the abscess is drained surgically or perforates spontaneously, it will give rise to a fecal fistula; such as vesico-sigmoidal fistula, enterocolic fistula, vagino-colonic fistula, pelvi-rectal fistula, or a combination of sigmoido-vesical and ileo-vesical fistula (50).

However, a hyperplastic type of inflammatory reaction is most commonly encountered. This is a condition of chronic extra-mucosal inflammation, the result of a leakage of toxins or bacteria through the mucosa, with the formation of a large mass consisting of large amount of fat and fibrous tissue. Micro-



scopically it is made up of granulation tissue cells. Giant cells may be found, and these must not give rise to a mistaken diagnosis of tuberculosis (19).

*The incidence of the diverticulitis of the colon.* Although most people with diverticulosis of the colon remain symptom-free, instances of diverticulitis with its complications are not rare. In 175 cases of diverticulosis of the colon reported by Wigand (17), 22 showed an inflammatory reaction. Smithwick (20) reported the incidence of diverticulitis being 25.1 per cent of 2400 cases of diverticulosis of the colon. Buie (21) in 1549 cases of diverticula of the sigmoid found that about half of these patients complained some time of symptoms which could be attributed to inflammatory or other activity in these deformities. Ochsner and Bagen (11) found an incidence of diverticulitis in 27 per cent of their cases. Forbes (13) states that approximately 17 per cent of the people afflicted with diverticulosis develop infection of the diverticula.

TABLE I

*The age incidence of diverticulitis in the series of patients presented*

	AGE						
	Up to 20 years	20-30	30-40	40-50	50-60	60-70	70 and up
Number of cases . . . . .	—	2	9	12	34	30	21
Percentage . . . . .	—	1.8	8.2	11	31.4	27	20.6

TABLE II

*The character of pain in the series of cases presented*

CHARACTER OF PAIN	NO. OF CASES	PER CENT
Acute pain . . . . .	31	28.7
Intermittent cramp-like pain . . . . .	54	50
No pain at present time . . . . .	23	21.3

*Age and sex incidence of diverticulitis of the colon.* The sex incidence of diverticulitis is variable. In our series, the distribution was practically equal; it occurred in 51 females and 57 male patients. In 100 cases studied by Spriggs and Marxer (9), 29 were women and 71 men.

Diverticulitis is said to be the disease of old age, but it is possible that it may be found more frequently than supposed in young adults. Bearse (22) stated, "Postmortem studies do not portray the true incidence of diverticulitis in young persons, since there is only an approximate mortality of 0.4 per cent of the population who are under 30 years of age."

*Clinical features of diverticulitis of the colon.* The clinical features of diverticulitis of the colon vary with the extent of the involvement and the location of the lesion. Simple acute diverticulitis may involve any portion of the colon but most commonly it occurs in the sigmoid-colon. It is frequently called "left sided appendicitis," because of the marked resemblance of the signs and symp-

toms to those of acute appendicitis (23), such as tenderness, rigidity and localized pain. Nausea and vomiting are not uncommon. There may be an elevation of the temperature and the white blood count, depending on the degree of inflammation present.

Pain is the most common symptom, ranging in severity from a slow boring type of discomfort to an intermittent sharp pain. Sometimes the history of pain may be completely absent, but in these cases there is generally chronic abdominal discomfort.

*Physical examination.* On physical examination, it is sometimes possible to find a tender mass, generally situated in the left lower abdomen. The presence and site of a mass depends upon the stage and location of the inflammatory process. The presence of the mass was noted in 32 cases in our series, in 25 of which the mass was located in the left lower abdomen.

TABLE III  
*The site of pain in the series presented*

SITE OF PAIN	NO. OF CASES	PER CENT
Lower abdomen . . . . .	37	43.5
Left lower abdomen . . . . .	25	29.4
Right lower abdomen . . . . .	13	15.2
Other locations . . . . .	10	12.9

TABLE IV

CHARACTER OF BOWEL MOVEMENT	NO. OF CASES	PER CENT
Normal bowel movement . . . . .	47	43.5
Constipation . . . . .	35	32.4
Diarrhea . . . . .	20	18.5
Intermittent diarrhea-constipation . . . . .	5	4.6
Change in the stool . . . . .	1	0.8

*Change in bowel habit.* Bowel habits previous to the acute onset of symptoms may be normal. Young (24) stated that there is no change in the bowel habit in 45 per cent of the cases. However, if such alteration is present, it may be either constipation, intermittent diarrhea-constipation or diarrhea. The change in the bowel habit in this series is shown in Table IV.

*Passage of blood from the rectum.* The occurrence of this symptom has been the subject of much discussion. Erdman (25) believes that the bleeding ascribed to diverticulitis of the colon does not exist. Having excluded the possibility of other sources of rectal bleeding, Willard and Bockus (26) reported the presence of occult blood in two cases of diverticulitis. Ochsner and Bagen (11) noted bleeding in five per cent of their patients. Bleeding from the bowel occurred in 44 patients of this series; in 35 the blood was occult and in 9 there was evidence of gross rectal bleeding. In 4 patients of the latter group, the bleeding was so

profuse as to require several transfusions. The complicating factors found in these 4 cases with profuse rectal bleeding were, rectal polyp in one patient, arteriosclerosis in the second patient and hypertension in the two others. Boekus (27) believes that the presence of occult blood in the stool has no clinical significance, if the dietary factor has been ignored. "The absence of occult blood in the stools in such cases is evidence of lack of bleeding, but the presence of occult blood may be misleading."

*Röntgen examination.* The x-ray appearance of diverticula of the colon may be discussed under three headings:

(a) The prediverticular state. This is characterized by the ragged outline of the wall of the bowel, which does not dilate even under the most favorable conditions. The importance of this condition has been debated by many authors.

(b) Diverticulosis. Diverticulosis may be demonstrated by the barium meal or the enema. If the latter is used, the post evacuation film is especially important, for the diverticula may be obscured by the barium distended colon. Occasionally, the diverticulum is not evident either on pre or post evacuation films, but may appear on the films taken the following day. The possible explanation may be that the barium fails to enter the inflamed diverticula or that the peristalsis is inadequate to force the opaque material into the sac. There are other shadows characteristic of this condition. If the pocket contains a fecalith, the barium surrounds it and casts a ring-like shadow. A similar pocket without a fecalith when filled with barium gives a bud-like shadow. Another characteristic of diverticula of the colon is the retention of the barium in the pockets for a number of days. This persistence justifies the diagnosis even in the absence of the above described characteristic shadows.

(c) Diverticulitis. The swelling and hypertrophy of the mucosa and muscularis secondary to the diverticulitis is outlined by the barium shadows. The intestine in the involved region are narrow and irregular, with a "saw-tooth" margin due to the deep mucosal folds which under the fluoroscope appears irritable, tending to expel its contents. Muscular spasm may be so marked that the enema fluid will not enter the involved region, producing an appearance of a complete obstruction. The important and at times difficult point is the differential diagnosis between diverticulitis and carcinoma. In a great majority of cases, the differential diagnosis can be made (28). The thickening of the mucosal folds which produces sharply irregular "saw-tooth" margins is quite different from the less irregular and sometimes smooth inner surface of the malignant constriction where the growth has invaded and destroyed the mucosa. Carcinoma is rigid while diverticulitis changes under the pressure of the fluid. Diverticulitis may cause a complete obstruction, in which case a differential diagnosis is almost impossible. In rare instances the complete obstruction may be due to spasm, in which case the examination may be repeated after administration of atropine or nitroglycerine to relax the spasm (29). An x-ray examination was performed in the whole series of cases presented. In 95 cases a barium enema was done and the diagnosis of diverticulitis of the colon made. In three cases the differential diagnosis between carcinoma and diverticulitis could not be



made and in 10 patients the barium enema could not be performed due either to a low colonic obstruction and spasm or the acute character of the disease contraindicated such a procedure.

*Proctoscopy.* Although the diagnosis of diverticulitis of the colon is dependent primarily on clinical and roentgenological studies, proctoscopic examination is at times valuable especially to rule out other conditions. In our series of 108 cases, sigmoidoscopy was performed in 69 patients. Fourteen showed one or more of the following signs: fixation, angulation of the bowel or spasm. Biopsy was taken only on two occasions. The pathological report in one was acute inflammation of the bowel-wall and the second case was diagnosed as a benign polyp. In 400 cases of diverticula of the colon studied by Jackman and Buie (30) sigmoidoscopic examination revealed some evidence of diverticulitis in 168 cases. In another group of 59 cases in which colostomy had been performed as an emergency measure because of an obstructing lesion in the lower part of the bowel, and in which the preoperative diagnosis was undetermined, sigmoidoscopic examination through the colostomy and the rectum was responsible for the diagnosis in 37 cases. Jackman and Buie (30) described the following proctoscopic signs in diverticulitis of the colon: 1. Limited mobility of the segment of the bowel which is normally freely movable. 2. Angulation of the bowel. 3. Sigmoidal sacculation.

*Complications of diverticulitis of the colon.* The following outlines the variety of complications generally encountered in diverticulitis of the colon:

1. *Sudden perforation.* Spontaneous perforation of diverticulitis of the colon into the free peritoneal cavity and generalized peritonitis is comparatively rare, but not infrequent. In our series of 108 cases there were only two cases of acute perforation of the diverticulum, an incidence of 1.8 per cent. In the series of 140 cases reported by Hayden (12) there were only three cases of sudden perforation of the diverticula. The clinical picture of this abdominal catastrophe includes shock, generalized abdominal pain, more pronounced on the site of the rupture, a silent and rigid abdomen and a mounting leucocyte count (see table VI). Colp (32) cites an unreported case in which the x-ray examination of the abdomen showed the presence of free air under the diaphragm.

2. *Slow perforation of chronic diverticulitis and abscess formation.* Slow perforation of the colonic diverticulitis with abscess formation is much more frequent than the spontaneous rupture. The site of the abdominal abscess generally depends upon the region of the bowel involved, and given the frequency of sigmoidal diverticulitis, the peri-colonic abscess is most encountered in the left lateral gutter and in the cul-de-sac. Occasionally subphrenic and subhepatic abscesses may be encountered; they are generally metastatic abscesses. Arnheim (33) in his review of the cases reported in the literature found that in 834 cases of diverticulitis, the incidence of rupture with abscess formation was 19 per cent.

In the series of cases presented there were 16 cases of slow perforation with local peritonitis. A localized abscess was found in 14 cases of which 9 were in left lower abdomen and 5 in the pelvis. The two other patients had metastatic

abscesses, one subphrenic and the second subphrenic and subhepatic abscesses (see table VI). The signs and symptoms of slow perforation of the diverticulitis are generally subacute, due to the fact that the perforation is quickly sealed off and the region rapidly immobilized and protected by omentum. The clinical signs and symptoms are a generalized toxicity including fever, leucocytosis; there may be evidence of an abdominal tender mass. Occasionally the purulent focus may rupture into the peritoneal cavity, in which case the previously described clinical picture prevails.

3. *Fistula formation.* There are varieties of fecal fistulae encountered secondary either to the spontaneous rupture of the colonic diverticula or following the drainage of peridiverticular abscess. The most common form of fistulae encountered are: entero-intestinal fistula, entero-cutaneous fistula, vagino-colic fistula, and entero-vesical fistula, the latter being the most common. Bockus (27) reports the case of perforation of diverticulum of the descending colon into the left ureter, in which the necropsy confirmed the diagnosis made following intravenous and retrograde urography. Hayden (12) reports a case of nephro-colic fistula.

In our series we found four cases of vesico-sigmoidal fistulae, one sigmoido-vaginal fistula, one perirectal fistula, and two cases of fecal fistula following laparotomy. Of all the surrounding structures the urinary bladder is the most common site for fistula development due to its location low in the pelvis and close to the sigmoid-colon.

The most common cause of a vesico-colic fistula is ascribed to diverticulitis of the colon. In a collective series of 328 cases reported by Higgins (34) an inflammatory lesion was the etiological factor in 160 cases, diverticulitis being the initiating cause in 57.5 per cent. Dobson and Moir (35) collected 46 cases of vesico-intestinal fistulae, of which 30 cases were secondary to diverticulitis of the colon. Kellogg (36) in 1938 discussed the condition in detail and summarized 592 cases reported until that time, 42 per cent in this series being secondary to diverticulitis of the colon.

Although slight variations due to the location of the primary lesion may be present, the general syndrome presented by patients with entero-vesical fistula is essentially constant. As a rule, they state that the condition was gradual in onset. Repeated attacks of lower abdominal pain and cramps, left hypogastric tenderness and change in the bowel habit. Later in the course of events, burning and frequency of urination occurs. Chills and elevation of the temperature complete the syndrome of entero-vesical fistula. With the establishment of fistula into the bladder, gas may be passed through the urethra, usually at the end of micturition, but the passage of feces does not occur as frequently as that of flatus. Pneumaturia, although helpful in diagnosis of fistula, is not pathognomonic. In fact, the passage of gas through the urethra may be due to catheterization, fermentation of urine in the bladder by yeast organisms, and in occasional cases of chronic infections of the renal pelvis or the bladder such as, *Escherichia coli*, *Aerobacter aerogenes*, or *Coccobacillus vesicae* (37) and (38). The actual demonstration of the fistula by means of x-ray and barium enema is difficult,

but should be possible if the opening is of sufficient size. Cystoscopic examination may be of some diagnostic value, where associated with previously described symptoms. The appearance will be an area of edema and inflammation in the fundus of the bladder.

4. *Peridiverticulitis and obstructive diverticulitis.* Peridiverticulitis with enterospasm, infiltration, and subsequent obstruction of the bowel, is the most common form of the disease. In cases reported by Rankin and Brown (39) this incidence was 31 per cent, McGrath (40) reported peridiverticulitis in 26 of the 27 cases of diverticulitis. This complication was present in 40 cases in our series or an incidence of 37 per cent. Thus there is a wide variation of different reports; however, most investigators agree that this incidence ranges between 20 to 30 per cent. The clinical picture consists of pain or cramps in the lower abdomen occasionally, a tender mass found on physical examination; a history of change in the bowel movement; and some times bleeding by rectum. In later stages, a partial or total intestinal obstruction may ensue, due to inflammatory hyperplasia, adhesions, or angulation of the colon. X-ray examination by use of fluoroscope and barium enema is the most valuable in the case of this type; it

TABLE V

	NO. OF CASES	TREATMENT	RESULT
Vesico-sigmoidal fistula . . . . .	2	Colostomy	Improved
Vesico-sigmoidal fistula . . . . .	1	Medical treatment	Unimproved
Vagino-sigmoidal fistula . . . . .	1	Transverse colostomy	Ceased
Fecal fistula following laparotomy . . . . .	2	Medical treatment	Improved
Pelvi-rectal fistula . . . . .	1	Medical treatment	Improved

will present a varying degree of spasm over a considerable length of the sigmoid, with "saw-tooth" appearance due to spasm of the circular muscles.

5. *Recurrent diverticulitis.* The recurrent attacks of diverticulitis almost invariably indicate the presence of some complications, the nature of which will vary in individual cases. In our series, 6 cases presented the symptoms of recurrent attacks, or an incidence of 5.3 per cent. The following complications were found on the second admission to the hospital: 2 cases of carcinoma, 1 case of ileus of the small bowel, and 3 cases of recurrent intra-abdominal abscess.

6. *Chronic diverticulitis.* In these cases, the normal physiology of the colon is altered by the presence of chronically inflamed diverticula, forming a mass, which may produce the symptoms of an intermittent intestinal obstruction. In this series, ten cases presented this complication, or an incidence of 9.2 per cent.

7. *Carcinoma.* Wybert (41) believes that 21 per cent of the sigmoid cancers originate upon the site of diverticula. Oschner & Bargaen (11) found malignancy of the colon in 6 per cent of the cases in which the diverticula of the colon were discovered by clinical examination. This association was noted only among the patients who had diverticulosis, and who did not give a history suggestive of diverticulitis. If there is a causal relationship between diverticulitis and

carcinoma, it has not been clearly demonstrated. It is safe to say that the relation of chronic inflammation to carcinoma is much the same in the bowel as it is elsewhere in the body. This was shown by Fallon (42) who reported the incidence of associated carcinoma being 0.5 per cent in a group of 625 cases of diverticulitis. In our series this incidence was 1.8 per cent.

*Diagnosis of the colonic diverticulitis.* The possibility of diverticulitis of the colon must be considered in a patient past forty years of age, with persistent intermittent lower abdominal pain, cramp, and flatulence, with periodic exacerbation of constipation or intermittent constipation and diarrhea. The diagnosis may be confirmed by x-ray findings. In complicated cases of diverticulitis, especially in cases in which there is suppuration, there will be a sudden acute pain, generally in the left lower abdomen, similar to the pain of acute appendicitis. Rigidity accompanies the pain; fever and leucocytosis are common. On physical examination a tender mass may be found.

*Differential diagnosis.* 1. Carcinoma. Diverticulitis may simulate carcinoma so closely that occasionally the differentiation is impossible, even at the operating table (43) for the diverticula are completely buried in the dense inflammatory mass. This makes it doubly important to have a preoperative diagnosis if at all possible and no effort should be spared to make one. The x-ray examination is of great help in this differentiation; in fact, the filling defect in carcinoma is limited to a narrower segment and fixed portion of the bowel, while the spasmodic bowel presents an inconstant filling defect. The long history of chronic constipation or intermittent constipation-diarrhea, the good general condition of the patient, the presence of fever and leucocytosis, are more in favor of diverticulitis. A malignant lesion in the recto-sigmoid may be seen through the sigmoidoscope and a biopsy may be obtained. Nevertheless, the possibility of error is great in this differential diagnosis. In Graham's (44) series of cases, an error in diagnosis was made in 29 per cent of cases of which 50 per cent were errors in differential diagnosis between diverticulitis and carcinoma. In the series presented, the error in diagnosis was made in 10 per cent of cases and of these 27 per cent were errors in differential diagnosis between carcinoma and diverticulitis of the colon.

2. Acute appendicitis. Two complications of diverticulitis of the colon may be confused with acute appendicitis. One is acute diverticulitis of the cecum, and the other is acute diverticulitis of a redundant sigmoid colon. These two conditions constituted 54 per cent of the errors in diagnosis in the series presented. A history of chronic indigestion associated with discomfort or a dull aching pain and cramp in the lower abdomen, with periodic exacerbation is suggestive of acute diverticulitis.

3. Hyperplastic tuberculosis of the colon. This condition is rare in the sigmoid colon (27) but occasionally occurs in the cecum. On the other hand, caecal diverticula are comparatively rare. The x-ray examination of the colon frequently shows diverticula.

4. Other disease conditions. Diverticulitis of the colon may very occasionally simulate some other diseases such as ulcerative colitis, ileocolitis, pelvic inflamma-



tory diseases and ovarian cyst or tumor, in which case the differentiation may readily be made by the clinical observations and the x-ray examination of the colon. If the rectal bleeding is the prime symptom, all the other possibilities should be excluded before attributing it as diverticular origin.

*Treatment of diverticulitis of the colon.* The treatment of diverticulitis has been subject to a great deal of controversy and confusion. In fact, there have been two schools of thought, the conservative and the radical. The former relies upon watchful waiting and symptomatic treatment; the latter believes in early surgical exploration. Lynch (45) advises surgery, "There is no medical treatment for diverticulosis, any more than there is any medical treatment that will abort appendicitis" and he further advised "all people with diverticulosis would be better off with appendicostomy; diverticulitis would be less likely to develop." Erdman (25) advises "The acute condition presents but one solution in the absence of contraindication, and that is early operation." On the other hand, Spriggs and Marxer (9) state "The removal of a diverticulous bowel has been recommended; if there is pericolitis with infection of the bowel wall and adhesions, this is surgically often neither safe nor possible. If there is not pericolitis, a favorable course of the disease does not justify such operation. Furthermore, there is no evidence that removing one part of the colon would prevent diverticulosis from arising in the remainder." Lockhart-Mummery (46) in reviewing the late results in diverticulitis, found that while patients who adhered strictly to a regime remained symptom-free, the number and size of diverticula kept increasing. Buie (21) believed that "A more conservative attitude should be observed in the treatment of diverticulitis. The diverticula does not swing in the abdominal cavity as does the appendix, and the rupture of diverticulitis with resultant general peritonitis rarely occurs." Hurst (48) stated that by medical treatment it is possible not only to cure the slight cases in which the question of surgery can hardly arise, but even to relieve severe cases in which obstructive symptoms and an acutely tender inflammatory mass accompanied by pyrexia and leucocytosis are present.

From therapeutic point of view, Jones (47) suggests to classify diverticulitis into three groups: diverticulitis with enterospasm, diverticulitis with infiltration, and diverticulitis with perforation; and advises the decision of medical or surgical treatment according to each group of the complication present. Pepper (51) states "Diverticulitis is a medical disease with surgical complications."

*Medical treatment of diverticulitis of the colon.* The medical treatment of colonic diverticulitis is based on the broad principles on which there is fairly uniform agreement (27).

1. Asymptomatic colonic diverticula. This requires no treatment, although certain prophylactic measures are necessary such as to have the bowel at rest by administration of a low residue diet and prevention of constipation by daily intake of laxatives such as mineral oil.

2. Diverticulitis with enterospasm and infiltration. The medical management consists of bed rest, institution of a diet low in residue and preferably liquid administered frequently in small quantities, and a daily warm saline enema, for

TABLE VI

CASE	AGE	SEX	HISTORY	PHYSICAL EXAMINATION	DIAGNOSIS	OPERATION	COURSE
385525	38	M	Acute lower abdominal pain with temp. 102. Chr. constipation	Abdominal distention, WBC 21,000	Acute pancreatitis?	I. & D. of subphrenic abscess due to ruptured diverticulitis of the colon	Similar attacks twice, treated medically. Well one year follow-up
499197	64	M	Complaining of diffuse rectal bleeding	Left lower quadrant mass	Carcinoma of sigmoid?	Obstructive resection of mass. Path. report: diverticulitis	Postoperatively patient had a wound rupture with generalized peritonitis and died
520825	55	F	Chr. lower abdominal pain started 4 months prior to admission. Progressive constipation. Temp. 100.4	Abdomen slightly distended and tender in both lower quadrants. Large, firm, irregular pelvic mass	Carcinoma of sigmoid?	Obstructive resection of mass; drainage of abdominal cavity. Path. report: diverticulitis	Improved. Colostomy closed 2 months later. No complaints
415178	39	M	Acute lower abdominal pain and nausea for 1 week. Rectal bleeding. Temp. 102	Right lower quadrant mass. Fecal fistula	Abdominal abscess	Incision and drainage of abdominal abscess	Improved. Fistula closed spontaneously. One yr. later, recurrent attack relieved by medical treatment. 4 yrs. later still some low abdominal discomfort
499197	64	F	Lower abdominal pain, bleeding from rectum. Normal temperature	Left lower quadrant mass of indefinite extent	Diverticulitis? Carcinoma?	Obstructive resection of mass. I. & D. of perisigmoidal abscess	On 5th p.o. day evisceration. Ceased on 9th p.o. day
434316	38	F	2 months low abdominal cramps, diarrhea, melena, mu- cus, weight loss	Rigidity and tenderness in lower abdomen. Left lower quadrant mass	Diverticulitis	Transverse colostomy	Improved. 9 months later colostomy closed. No complaints

154457	50	F	Right lower quadrant pain started 2 days ago with rise in temp. to 101. Constipation	Localized tenderness in the right lower quadrant	Acute appendicitis?	Exploratory laparotomy. P.O. G.I. series; diverticulitis of hepatic flexure	Improved. 1 year later patient admitted for r.u.q. cramp pain. Improved by medical treatment
489598	59	F	Chronic lower abdominal pain. Rise in temp. to 101	Left lower quadrant tender mass	Perforated diverticulitis of colon	I & D of abdominal abscess	Readmitted for I & D of recurrent abdominal abscess. Follow-up: No complaints. Abd. mass still present
450332	80	F	Acute low abdominal pain starting 18 hours ago. Vomiting, black stool mixed with pus. Temp. normal	Abdomen slightly distended. Tenderness in both lower quadrants	Diverticulitis of sigmoid	Cecostomy under local anesthesia	Improved. Readmitted one month later for low abdominal pain, relieved by medical treatment
533041	68	F	4 months lower abdominal pain and pain on micturition. Temp. to 104. Passage of feces and gas through urethra	Left lower quadrant mass. Vesico-colic fistula; previous non-functioning colostomy	Diverticulitis of sigmoid	Complete diverting colostomy	Improved
460302	63	F	Acute lower abdominal pain with a history of intermittent constipation and diarrhea, blood in stool. Vesico-colic fistula. 15 lbs. weight loss	Left lower quadrant tenderness. Abdomen distended. Symptoms of intestinal obstruction	Diverticulitis? Carcinoma?	1st stage transverse colostomy. 2nd stage obstructive resection of mass, closure of bladder fistula	Colostomy functioning well. One attack of pain relieved by medical treatment. Improved since

TABLE VI—Continued

CASE	AGE	SEX	HISTORY	PHYSICAL EXAMINATION	DIAGNOSIS	OPERATION	COURSE
486671	49	M	Acute lower abdominal pain; chill, and fever up to 104	Left lower quadrant rigidity; tenderness in both lower quadrants	Perforated diverticulitis of sigmoid. Localized peritonitis	I. & D. of subhepatic and subphrenic abscess	Uneventful recovery. Discharged. Re-admitted 7 months later for intestinal obstruction. Exploratory laparotomy showed volvulus of small bowel and gangrene. Resection performed. Patient ceased p.o.
513892	51	F	Acute right lower quadrant pain, 1 month previous to admission. Pain became more severe day before admission. Weight loss 5 lbs. Temp. 102	Right lower quadrant tenderness. Abdomen distended. Low abdominal mass tender on palpation	Twisted ovarian cyst? Carcinoma of sigmoid? Diverticulitis?	I. & D. of perisigmoidal abscess; obstructive resection of mass. Glass rod colostomy proximal to lesion.	One year later, no complaints. Colostomy was closed
375348	28	M	Acute right lower quadrant pain, vomiting, rise in temp. 12 hrs. History of previous attacks 7 months ago	Symptoms of generalized peritonitis	Acute perforated appendicitis	Primary closure of perforated diverticulitis of sigmoid with drainage	Well
435850	32	M	Generalized abdominal pain, 12 hours duration especially in r.l.q. Nausea	Rigidity and tenderness in right lower quadrant. Temp. 101.6	Acute perforated appendicitis	Primary closure of perforated diverticulitis of cecum	Well



379995	26	F	Acute low abdominal pain of 34 hours duration. Bilat. at onset, mostly r.l.q. on admission. History of previous attack	Lower abdominal mass. Symptoms of acute intestinal obstruction. Temp. 101	Acute appendicitis	I. & D. of intra-abdominal abscess due to ruptured diverticulitis of sigmoid. Appendectomy	Re-admitted 3 times for symptoms of abdominal abscess treated by I. & D. Since last admission patient feels fine
480580	58	M	Acute right lower quadrant pain 1 day's duration with rise in temperature	Lower abdominal tenderness, more marked in r.l.q.	Acute appendicitis	Exploratory laparotomy. Drainage of abdominal cavity for inflamed sigmoid	Improved
525806	72	F	Vagino-sigmoidal fistula for 1½ years. No previous abdominal symptoms	No positive findings except for fistula which can be probed several centimeters	Enterovaginal fistula due to diverticulitis?	Transverse colectomy	Patient ceased with symptoms of purulent peritonitis and pulmonary embolism
507387	32	F	Intermittent left lower quadrant pain 2 weeks, relieved by cathartic but since night before, pain became worse	Left lower quadrant tenderness	Tubo-ovarian abscess?	Exploratory laparotomy	Postoperatively patient had a fistulous tract which sealed off spontaneously. Patient improved
527537	63	F	6 weeks right lower quadrant pain, rise in temp. to 100.8. Similar attacks 2-3 years ago. Loss of 15 lbs.	Tender right lower quadrant mass. Count 9 000 with shift to left	Peri-appendiceal abscess? Diverticulitis of sigmoid?	Exploratory laparotomy with drainage of peridiverticulitis of sigmoid	Improved

the purpose of softening and encouraging liquefaction of any stercoliths that may have formed in the diverticular sac. Antispasmodics and sedatives such as belladonna and phenobarbital are given by mouth. In acute cases with partial intestinal obstruction, and dehydration due to vomiting, the patient may require parenteral fluid, and hypodermic injection of sedatives and antispasmodics. Although the Miller-Abbott tube is of doubtful value in relief of sigmoidal obstruction, it has to be attempted to prevent small intestinal distention. After the patient recovers, the diet would be the same as prescribed for the asymptomatic type of diverticula.

*Surgical treatment of diverticulitis of the colon.* The surgical treatment of diverticulitis should be reserved for such complications as acute perforation, formation of a peridiverticular abscess, inflammatory obstruction, or fistula. The type of operation indicated depends on the complication present.

1. Acute perforation. Whether to attempt an immediate operation or to wait for localization of the pathologic process, depends on the individual case. In most cases the fulminating character of the clinical picture of acute diverticular perforation justifies laparotomy. Generally a definite diagnosis may be made only at operation. The opinion varies concerning proper surgical procedure; some authorities advocate the simple closure of the perforation or removal of the diseased diverticula before closing the perforation and drainage of the involved area. Some others prefer exteriorization of the loop of the bowel bearing the ruptured diverticula. Some surgeons advise not to attempt closure of the perforation, but simply drain the area of the rupture. A sudden perforation into the free peritoneal cavity occurred in 2 of the 108 cases in this series. Simple closure of the perforation was performed and the abdominal cavity was drained; both patients had an uneventful recovery (see table VI).

2. Slow perforation with peridiverticular abscess formation. This is the most common surgical complication. The opinion varies concerning the proper treatment to be undertaken. Some authors prefer the nonoperative treatment of the abdominal abscess in the hope of spontaneous resolution of the process, some others advise surgical intervention, evacuation and drainage of the abscess. Usually surgical treatment is preferred, when the diagnosis has been established. Peridiverticular abscess occurred in 7 of 108 cases presented. One was treated (in one stage) by incision and drainage of the abscess, obstructive resection of the mass and a transverse colostomy over a glass rod and the patient made an uneventful recovery. The second patient was treated by incision and drainage of the abscess and obstructive resection of the inflammatory mass. Rupture of the wound and evisceration occurred on the 5th post-operative day and the patient ceased on the 9th postoperative day. The five other patients were treated by simple incision and drainage of the abdominal abscess. All these patients had recurrent attacks of diverticulitis and recurrent abdominal abscesses. Three of these patients required repeated incision and drainage of which two improved and one ceased after the second intervention. The two other patients of this group responded favorably to conservative treatment (see table VI).

3. Obstructive diverticulitis. If the obstruction is the prime symptom, it

has to be treated surgically. The Miller-Abbott tube is indicated to prevent small intestinal distention. The surgical procedure entails a side-tracking of the fecal content far enough from the site of the obstructive lesion, i.e., transverse colostomy in case of a lesion in the sigmoid or cecostomy if the lesion is in the transverse or ascending colon. Cecostomy is indicated only in a very sick patient as the simplest method to relieve the obstruction. It is preferable to employ a spur colostomy so as to divert completely the fecal stream and permit a through and through irrigation of the distal portion of the bowel. The resolution in some instances is so complete that one is tempted to consider closure of the colostomy without further surgical interference. Kerr (48) believes that although colostomy is the procedure of choice in some cases the incidence of recurrence of symptoms is sufficiently great to justify a more radical procedure such as bowel resection following primary colostomy. Hayden (12) enumerates several factors justifying radical surgery; namely, recurring obstruction and fistula formation, the possibility of perforation during further acute attacks and the ever present possibility that the obstruction may actually be due to cancer rather than diverticulitis, or to a co-existence of both conditions. Rankin and Graham (49) believe that resection must be undertaken only for urgent reasons, and its performance is more hazardous than a resection in the presence of carcinoma. It is sometimes technically possible to perform a resection of the inflammatory mass without a preliminary colostomy, but it is wiser not to attempt such a procedure. A spur colostomy should practically always precede resection. After several weeks interval, during which time by daily irrigation of the defunctioned distal bowel the inflammation subsides and the mass reduces in size, a resection may then be attempted and continuity re-established, either by end-to-end anastomosis or by a Mikulicz type of obstructive resection. In the series presented, acute abdominal obstruction requiring immediate surgical intervention occurred in four cases. Cecostomy was performed in one case, which then closed spontaneously and the patient presented a recurrent attack of diverticulitis a month later. This was treated medically. On the second patient a transverse colostomy was performed, followed at a second stage by an obstructive resection of the inflammatory mass. The colostomy was closed at a later date and the patient has been symptom-free ever since. In two other patients an obstructive resection of the mass and a transverse colostomy were performed, all in one stage; these two patients had an uneventful recovery (see table VI).

4. *Fistula formation.* The treatment of fistula secondary to diverticulitis of the colon is a surgical problem and each case requires individualization. Most of the fistulae following laparotomy subside spontaneously when the inflammation of the bowel-wall resolves. Some may require diversion of the fecal stream by means of a spur colostomy far enough and proximal to the internal opening of the fistula. After a sufficient lapse of time and when the inflammation is completely subsided, the removal of the fistulous tract may be attempted.

*Sigmoido-vesical Fistula:* A survey of the existing literature yields a number of methods used in the surgical treatment of the sigmoido-vesical fistula secondary to diverticulitis. Experience has shown that the three-stage operation has

much to recommend it, and will probably be the operation of choice in most instances. The first stage consists of a complete diverting proximal colostomy. The major operation is carried out some time later and consists of separation of the diseased bowel from the bladder, repair of the bladder fistula, and resection of the diseased segment of the colon. The final stage is an extraperitoneal closure of the colostomy. Free drainage of the urinary bladder during the treatment is essential. This may be achieved by either a suprapubic cystotomy or an indwelling catheter. Table V represents the different forms of fistulae encountered in our series of cases and the treatment undertaken, with the results obtained:

Twenty cases of complicated diverticulitis of the colon requiring surgical intervention are abstracted and reported in Table VI.

#### SUMMARY

One-hundred eight cases of diverticulitis of the colon admitted to the ward services of the Mount Sinai Hospital, New York, during the twelve-year period between 1933 and 1945, are reported. Of these patients, 51 were female and 57 male. The age of the patients ranged between 29 to 90 years, but the maximum incidence of diverticulitis was encountered between 50 and 60 years of age.

On physical examination, an abdominal mass was found in 29.6 per cent, of which 78.1 per cent were situated on the left lower abdomen. Change in bowel habit was present in 56.5 per cent. Bleeding from the bowel occurred in 44 patients, in 35 the blood was occult and in 9 there was evidence of gross bleeding; in this group 4 patients presented a profuse rectal bleeding requiring several transfusions. The complicating factors found in this group were: rectal polyp in one patient, arteriosclerosis in the second patient, and hypertension in the two others.

The following complications were encountered in this series:

Sudden perforation . . . . .	1.8%
Slow perforation with abscess formation . . . . .	14.8%
Peridiverticulitis and obstructive diverticulitis . . . . .	37%
Recurrent diverticulitis . . . . .	5.3%
Chronic diverticulitis . . . . .	9.2%
Carcinoma . . . . .	1.8%

The surgical treatment was undertaken in 20 patients, in whom either the diagnosis of diverticulitis was not certain or such complications as perforation, pericolic abscess, intestinal obstruction, fistulae were present. The different methods of surgical treatment instituted in this group of patients and the results obtained are summarized in Table VI.

The following table presents the final result of surgical and medical treatment in this group of 108 cases of diverticulitis of the colon presented:

RESULT	NO. OF CASES	PER CENT
Improved . . . . .	82	75.9
Unimproved . . . . .	19	17.5
Ceased . . . . .	7	6.6



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## THE "TWO-STEP" AND THE "ANOXEMIA" TESTS

### CASE REPORT OF A PATIENT WITH CORONARY ARTERY DISEASE AND NORMAL ELECTROCARDIOGRAM

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Coronary insufficiency occurs when the myocardial demand for blood or oxygen exceeds the supply. Since the primary cause of many, perhaps most, cases of angina pectoris of effort is sclerosis of the coronary arteries, it is this condition with which we are concerned.

In the majority of cases of angina pectoris, a definitive diagnosis can be reached by means of the history, physical examination, roentgen ray examination, and electrocardiogram. In about one-fourth of all cases of angina pectoris, however, examination fails to reveal abnormality of the heart (1). Montgomery, Dry and Gage (2) report that in a series of 405 patients with angina pectoris due to coronary sclerosis, who survived for ten or more years, electrocardiograms were normal in 236 (58.3 per cent) at the time the diagnosis was first made. Subsequent electrocardiograms made in 154 of these patients were normal in 67, or 70 per cent. These authors also point out that in half of the cases which exhibited abnormal deviations in the first examination, normal electrocardiograms were found at later examination.

To provide additional means for determining the capacity of the heart in patients with angina pectoris of arteriosclerotic origin, supplementary tests have been devised to measure or to detect the presence of actual or latent coronary insufficiency. The tests most commonly used are: Master's "2-step" exercise test (3, 4), and Levy's "anoxemia" test (5, 6, 7). The "2-step" test increases the work of the heart, and thereby, the myocardial demand for oxygen. The "anoxemia" test decreases the supply of oxygen. Basically, both tests produce a greater or lesser degree of ischemia or anoxia of the cardiac musculature. Both procedures depend upon electrocardiographic changes, particularly T-wave and RS-T changes, for the objective evidence of coronary insufficiency.

In the "2-step" exercise test, the patient does a standard amount of work in a specific time, the work consisting merely of walking up and down a standard "2-step" device, for a minute and a half, the number of steps varying with the sex, age and weight of the patient. The number of trips have been standardized in such a manner that with the production of a modicum of cardiac anoxemia in cases of coronary artery disease sufficient objective electrocardiographic evidence of coronary insufficiency is obtained while patients free of coronary artery disease show insignificant changes if any with the same number of trips. Standard electrocardiographic leads 1, 2, 3 and precordial lead CF<sub>4</sub> (mid-clavicular line in the fifth left intercostal space) are taken before exercise, immediately after exercise, and again at the end of two, five, and ten minute intervals.<sup>1</sup>

<sup>1</sup> The Sanborn "Viso-Cardiette," which was employed in these tests, made it possible to follow easily the sequential pattern of events during the tests.

In the "anoxemia" test (8), the patient breathes a mixture of 10 per cent oxygen and 90 per cent nitrogen for twenty minutes or until the onset of pain, if pain appears before the end of the twenty minutes. Standard electrocardiographic leads 1, 2, 3 and precordial lead IV F (apex) are taken before the test is started, at the end of 10- and 20-minute intervals of anoxia, and again following administration of 100 per cent oxygen for one minute and room air for five minutes. Tracings are often made also at the end of 5 and of 15 minutes of the anoxia.

The criteria for the "2-step" exercise test (4) are as follows (the presence of one provides evidence of coronary insufficiency): 1) Using the P-R interval of the electrocardiogram as the control or isoelectric level, depression greater than 0.5 mm. of the RS-T segment below this level in any lead. 2) A change from an upright T-wave to an isoelectric (flat) or inverted T-wave, or a change from a



FIG. 1. S. F., man, 51. Angina pectoris on effort for seven years. Teleoroentgenogram, February 26, 1947. Equivocal cardiac enlargement.

negative to a positive T-wave. 3) Premature beats or more significant arrhythmia, widening of the QRS, large Q waves, prolongation of the P-R interval, and heart block.

The criteria for the "anoxemia" test (8) are as follows (the presence of one is evidence of coronary insufficiency): 1) An arithmetical sum of the RS-T deviations in the four leads employed (1, 2, 3 and 4 F) totaling 3 mm. or more. 2) Partial or complete reversal of the T-wave in lead 1, accompanied by an RS-T deviation of 1 mm. or more in this lead. 3) Complete reversal of the direction of the T-wave in lead IV F, regardless of any associated RS-T deviation in this lead.

The following case illustrates the result of the two tests in a patient with angina pectoris of seven years duration, whose resting electrocardiograms had been normal during that period.



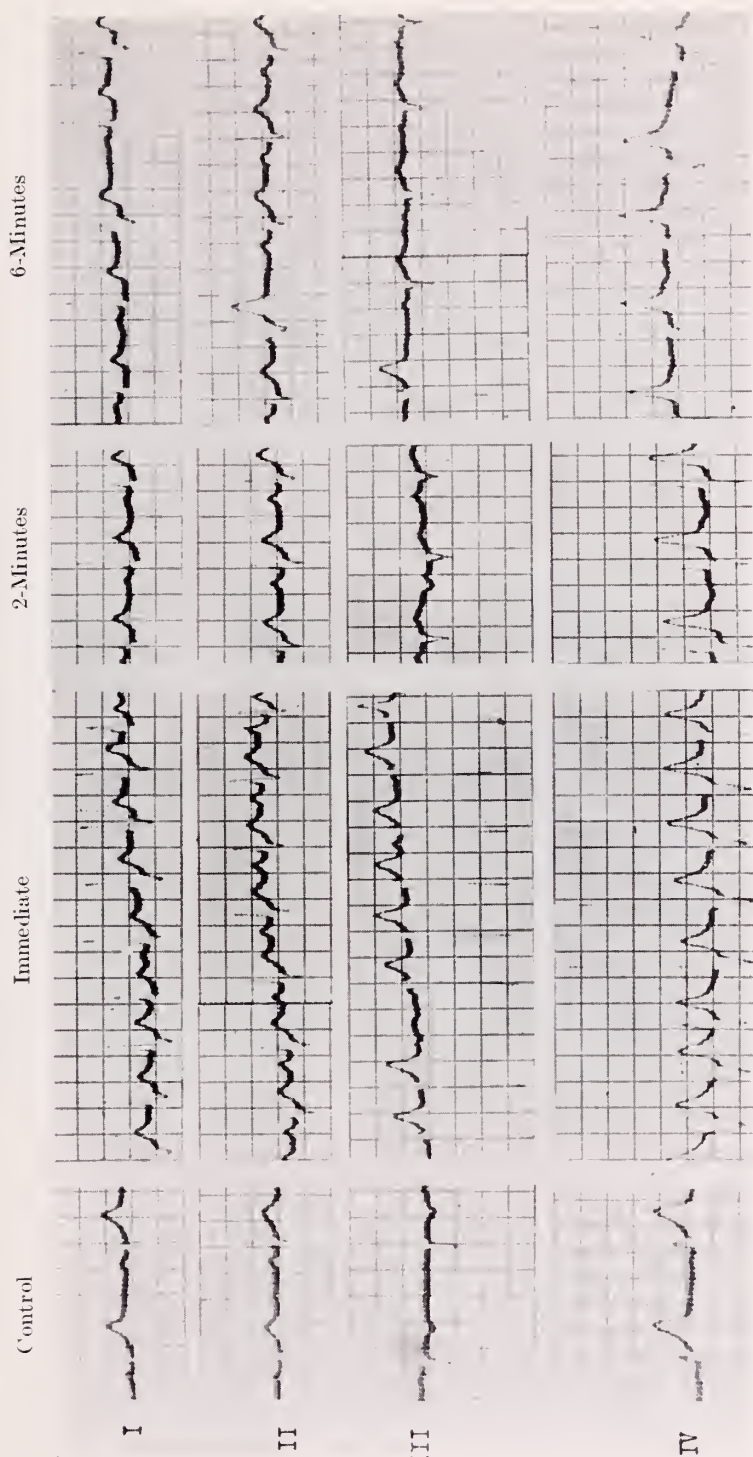


FIG. 2. S. F., man, 51. Angina pectoris on effort for seven years with normal electrocardiogram. February 5, 1947. Control electrocardiogram normal but E.C.G. after "Master 2-step" abnormal. RS-T and RS-T<sub>4</sub> depressed and a paroxysm of ventricular tachycardia immediately following effort. RS-T<sub>1</sub> depressed and occasional ventricular premature beat 2 and 6 minutes after the exercise.

A man (S. F.) was first seen in November, 1940, at the age of 44. He complained of pain in the chest when he walked in cold weather. His mother had died of "high blood pressure," and a brother had dropped dead of a "heart attack" at the age of 46. The patient's blood pressure was known to have been slightly elevated for the preceding eight years. He weighed 152 pounds and was 60 inches in height. He was fairly well nourished and developed, semi-bald, with a tinge of gray in his hair. Examination revealed a short systolic murmur at the apex and a moderately accentuated second aortic sound. His blood pressure on two occasions was 174/110 and 170/110 mm. Hg. The retinal vessels did not show any

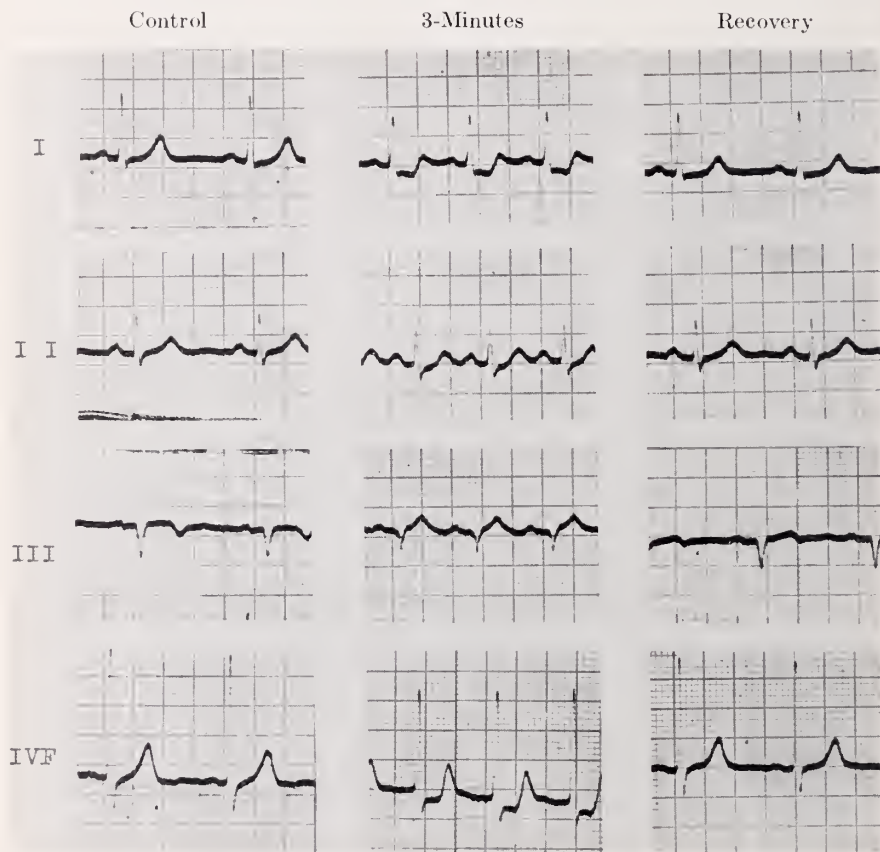


FIG. 3. S.F., man, 51. Angina pectoris on effort for seven years with normal resting electrocardiograms. Anoxemia test, February 8, 1947. Chest pain at  $4\frac{1}{2}$  minutes of anoxemia. Positive test for coronary insufficiency.

abnormality. After eating, on walking, and on exposure to cold, he felt knifelike pain under the sternum. This pain never lasted for more than a minute or two, and disappeared with rest. The patient was extremely nervous and said he had always been so. When excited, his blood pressure rose as high as 194/110 mm. Hg. The teleroentgenogram was normal. Electrocardiograms made following the time the patient was first seen, were consistently normal.

The patient was seen again in December, 1946. The substernal pain was occurring much more frequently and with much less provocation. Slight effort, excitement, or exposure to cold brought on pain. The pain did not last for more than a minute or two and it was relieved with rest. Circumnasal and circumoral pallor was noted, it was particularly promi-

nent when nervous tension was high. The physical examination again was irrelevant. A teleroentgenogram showed equivocal cardiac enlargement (fig. 1). All electrocardiograms were normal (see control tracings, fig. 2 and 3).

On February 5, 1947, the "2-step" exercise test was given this patient (fig. 2). The tracing preceding the test was normal. In the tracing immediately following exercise there

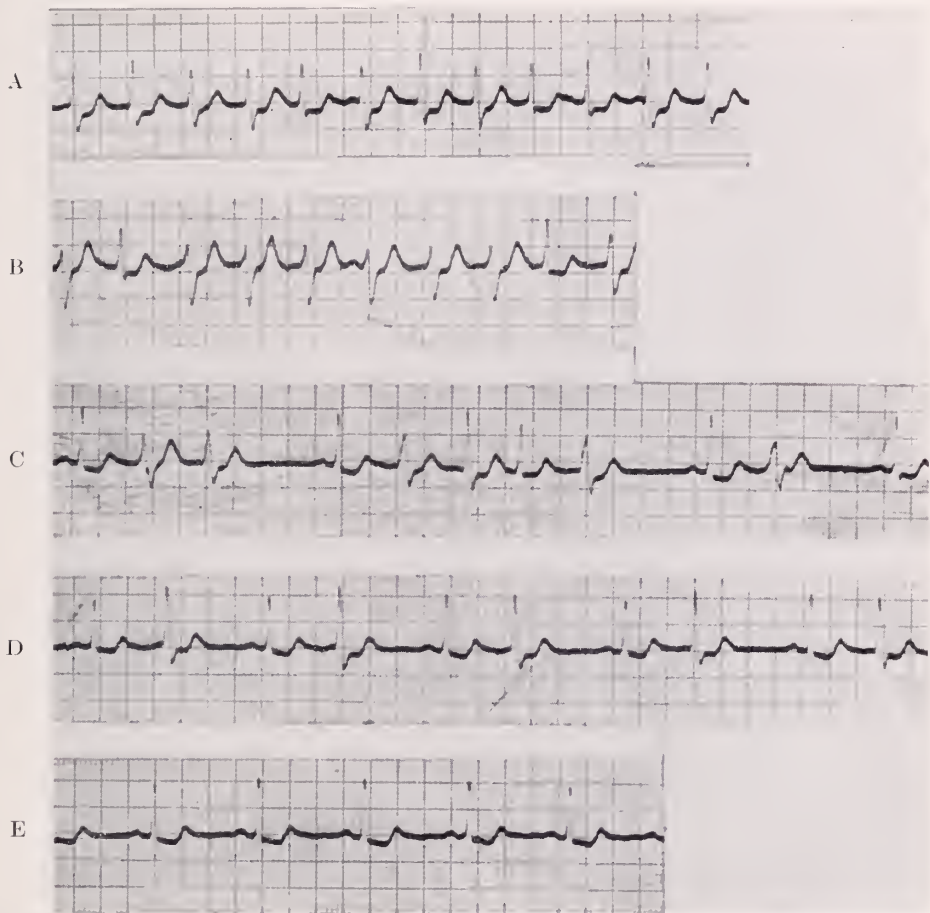


FIG. 4. S. F., man, 51. Angina pectoris on effort for seven years with normal resting electrocardiograms. Anoxemia test, February 8, 1947.

- A: at 3 minutes of anoxemia.
- B: at 30 seconds of 100 per cent oxygen.
- C: at 45 seconds of 100 per cent oxygen.
- D: at 60 seconds of 100 per cent oxygen.
- E: after 1 minute of room air.

were RS-T depressions of more than 0.5 mm. below the isoelectric level in leads 1 and 4, and intermittent ventricular tachycardia in these leads and in lead 3. Two minutes after the end of exercise, the tracing disclosed RS-T depressions of more than 0.5 mm. in leads 1 and CF4. In the 6-minute tracing RS-T depressions of more than 0.5 mm. appeared in lead 1, with premature ventricular contractions in all leads. These electrocardiographic deviations confirm the diagnosis of coronary insufficiency.

On February 8, 1947, the patient was given the "anoxemia" test (fig. 3). The pre-

liminary tracing was normal. In the record made at the end of 3 minutes of anoxia, the sum of the RS-T deviations in the four leads was more than 3 mm., and the T-wave in lead I became diphasic while the S-T depression in lead I was more than 1 mm. At the end of four and one-half minutes of anoxia, mild, slowly progressive substernal pain developed, similar to the pain experienced on effort. The electrocardiogram taken at the end of five minutes of anoxia was again positive for coronary insufficiency by the criteria previously listed. The test was terminated because of the chest pain.

Quantitative comparison of the electrocardiograms obtained in the two tests shows that the deviations correspond closely. In both procedures, the RS-T depressions were most marked in leads I and 4. In the "2-step" test, in lead I, there were RS-T depressions below the isoelectric level of 1.0 mm., 1.0 mm., and 0.75 mm. in the immediate, the 2-minute, and the 6-minute tracings, respectively; in the "anoxemia" test, depression in this lead at the end of 3 minutes of anoxia was 1.5 mm. In lead 4, in the "2-step" test, there were RS-T depressions of 1.0, 1.5, and 0.5 mm. in the immediate, in the 2-minute, and in the 6-minute tracings, respectively; in the "anoxemia" test, RS-T depression at the end of 3 minutes of anoxia was 1.5 mm. In both procedures, the T-wave which was initially inverted in lead 3, became upright.

During the "anoxemia" test, as in the "2-step" test, intermittent ventricular tachycardia appeared. The series of tracings is shown in figure 4: Tracing A, taken at the end of three minutes of anoxia, reveals 3-cycle and 6-cycle runs of ventricular tachycardia. Tracing B, taken following inhalation of 100 per cent oxygen for thirty seconds, reveals 6-cycle runs of ventricular tachycardia. In Tracing C, taken following inhalation of 100 per cent oxygen for forty-five seconds, may be seen pulsus trigeminus followed by pulsus bigeminus, caused by premature ventricular beats. Tracing D, taken following inhalation for one minute of 100 per cent oxygen, reveals pulsus bigeminus. In Tracing E, taken after one minute of rest in room air, regular sinus rhythm has been restored.

#### DISCUSSION

Many patients with angina pectoris due to coronary arteriosclerosis have normal electrocardiograms over long periods of time. Despite the fact that the substernal pain suffered by these patients usually appears following effort, emotion, heavy meals, cold weather, or combinations of these factors, electrocardiograms are customarily made when the patients are in a resting state. Yet, from the physiological point of view, it is apparent that electrocardiographic indicators of coronary insufficiency are more likely to become evident in tracings made following exercise than in those made when the patient is resting. This physiological consideration is taken into account directly in the "2-step" exercise test, and indirectly in the "anoxemia" test, which accomplishes the same end by reducing the supply of oxygen to the cardiac musculature. Both procedures, the first by increasing the demand for oxygen, the second by decreasing the supply of oxygen, rely on production of a greater or a lesser degree of ischemia in the cardiac musculature. The degree of ischemia produced depends largely on the patency of the coronary vessels.

It should be remarked that the tests had no untoward effects, except for the mild, slowly progressive precordial discomfort that the patient experienced during the "anoxemia" test. This discomfort completely disappeared following inhalation of 100 per cent oxygen for 45 seconds.

The cardiac manifestations of coronary insufficiency produced by the two tests fall into three patterns: 1) Temporary ischemia of the cardiac musculature,



manifested by RS-T deviations and T-wave changes. 2) Various arrhythmias, from ectopic beats to tachycardias. 3) Combination of (1) and (2).

Almost all the cardinal electrocardiographic deviations indicative of coronary insufficiency were presented in response to the tests. It is also noteworthy that, although the criteria for the two tests are different, the quantitative electrocardiographic changes presented by the patient were similar with both procedures in our patient, and in each instance were most marked in lead I and the precordial lead.

It should be emphasized that while the "positive" electrocardiographic signs indicate coronary insufficiency, it does not necessarily follow that the coronary arteries have undergone pathological change. Coronary insufficiency is not synonymous with coronary arteriosclerosis, although sclerosis of the coronary artery is commonly the etiological factor underlying coronary insufficiency.

#### SUMMARY

The "2-step" exercise test and the "anoxemia" test were given to a 51 year old man, with a history of angina of effort of seven years duration. During this period the findings on physical, roentgenographic and electrocardiographic examination were normal or equivocal. On the basis of the criteria employed for each procedure, the response to the tests was positive for coronary insufficiency. The quantitative electrocardiographic changes produced by the tests were almost exactly the same. Ventricular tachycardia developed during both procedures.

Master's "2-step" exercise test and Levy's "anoxemia" test are two tests used to detect coronary insufficiency, particularly in the presence of normal physical, roentgenographic and electrocardiographic findings. Both tests are based on ischemia, relative or absolute, of the cardiac musculature.

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# CEREBRAL AIR EMBOLISM COMPLICATING STELLATE GANGLION BLOCK<sup>1</sup>

MILTON H. ADELMAN, M.D.

The past decade has witnessed the rapid development and widespread application of therapeutic, diagnostic and prognostic nerve blocks. Chemical block of the stellate ganglion has been applied to the treatment of the following conditions (1): cerebral vasospasm; angina pectoris; paroxysmal tachycardia; asthmatic crises; acute pulmonary edema; acute and chronic circulatory disturbances of the upper extremity including thrombophlebitis, arterial embolism, reflex arteriospasm, acute vaso-spastic states, hyperhydrosis and post traumatic edema and osteoporosis; pain in the upper extremity and head, including causalgia, atypical facial neuralgia and phantom limb pain; and post-traumatic nerve palsies of the upper extremity.

The literature attests to the fact that such nerve blocks are not without risk. The reported dangers and complications of stellate ganglion block include pneumothorax (2), subarachnoid penetration and block (3), hemoptysis (1a), intravenous injection (1a) and sudden death (4). Inasmuch as the literature does not mention the complication of cerebral air embolism, the following case merits recording.

## CASE REPORT

The patient, M. D., a woman, aged 43, was admitted to The Mount Sinai Hospital as an ambulatory patient on March 8, 1947 for a diagnostic block of the right stellate ganglion. She complained of intractable pain of 6 years' duration localized in the right temporal, maxillary and mandibular regions. The patient described the pain as constant, deep-seated, throbbing and burning. In the course of the six years, the patient had been seen and treated ineffectively by Gasserian ganglion blocks and resections of portions of the right superficial temporal and right facial arteries. Psychiatric studies failed to reveal any functional basis for the complaints. It was decided that a diagnostic block of the right stellate ganglion was warranted because of the remote possibility that the atypical facial and head pain was based upon some dysfunction of the sympathetic nervous system.

The procedure was performed with the patient in the upright position. The anterior approach<sup>2</sup> was used. Because the deep bony landmark could not be reached, the needle was withdrawn and a longer needle was called for by the operator. A few seconds after the needle was removed the patient began to fall backward, obviously in syncope. At the same time, she began to cough and expectorate bright red blood. The patient was promptly placed in Trendelenberg position. She was comatose and her condition appeared grave; the breathing was of a stertorous nature and slight cyanosis was present. The skin was cool and moist. Pupils were equal and widely dilated, total flaccidity of all extremities was observed, and all reflexes were absent. The pulse was slow, 30 per minute, and the blood pressure was 120 systolic and 70 diastolic.

<sup>1</sup> From the Department of Anesthesia, Mount Sinai Hospital, New York City.

<sup>2</sup> A skin wheal is made with 1 per cent procaine at a point 1 cm. medial and above the midpoint of the clavicle. A 22 gauge 80 mm. needle is inserted, perfectly horizontal, and 45 degrees to the midsagittal plane, until bone is reached. The point of the needle thus lies in the region of the head of the first rib. After careful aspiration in two planes, 10 cc. of 1 per cent procaine is injected.

Oxygen (100 per cent) was immediately administered from an anesthetic machine. The patient was kept in Trendelenberg position and her oropharynx was cleared repeatedly of blood by the use of suction. Because of the marked bradycardia, a vago-vagal reflex was considered as a factor contributing to the clinical picture; therefore, 15 mgms. of ephedrine sulphate was administered intravenously while atropine was prepared for intravenous injection. The pulse increased promptly to within normal limits.

The cough and hemoptysis persisted for five minutes, during which time the patient's color improved and the breathing became less stertorous. About ten minutes after the onset of this episode, the patient began to manifest the return of various reflexes; ocular movements appeared soon to be followed by movements of the head and of the left upper and lower extremities. Five minutes later the patient was able to respond, somewhat slowly, to questioning by the operator. Speech returned about twenty minutes after the onset of this episode and the patient complained of inability to move the right upper and lower extremities. Examination revealed complete flaccidity of both right extremities and a right facial palsy. Examination for sensory disturbances was not made. At this time, the pulse rate and the blood pressure were within normal limits. The patient was kept at complete rest for another hour. During this interval the paresis in the right extremities disappeared completely, as did the right facial palsy. Examination of the chest showed no evidence of a pneumothorax. When the operator was satisfied that recovery was complete, the patient was permitted to return home.

Three days later the patient returned for another attempt at stellate ganglion block. This time the posterior approach<sup>3</sup> was used, and a successful block was performed without any untoward sequelae but without any significant relief of the patient's complaints.

#### DISCUSSION

The fresh hemoptysis, coma, and transient hemiplegia leave little doubt as to the diagnosis of cerebral air embolism. The case herein reported is another episode of cerebral air embolism following thoracentesis. However, it is unique in that it complicated a stellate ganglion block. The subject of air embolism during thoracentesis is too well known to require repetition here, yet one must emphasize the exceedingly small amount of air necessary to produce cerebral air embolism. Schlaepfer (5) has shown that as little as 1 cc. of air injected into a pulmonary vein of a dog can be fatal, in contrast to the large amounts of air that can be injected into a systemic vein without untoward effect. Thus, it is easy to visualize how minor trauma to the lung parenchyma may result in air embolism. Schlaepfer (5) also demonstrated a greater incidence of cerebral air embolism in the upright position, as compared to the horizontal position. In this patient the upright position was used and probably contributed to the reported complication.

This case seems to offer a major argument against the use of the anterior approach to the stellate ganglion. Pneumothorax with penetration of the lung

<sup>3</sup> A skin wheal is raised with 1 per cent procaine at a point 4 cm. from the spine of the seventh cervical vertebra. A 10 cm. 20-22 gauge needle is inserted perpendicularly to the skin until the head of the first rib, or articulating transverse process, is reached, usually at a depth of 2-5 cm. The point of the needle is then manipulated to the lower border of the rib, or transverse process, until it slips off the bone. It is then inserted at an angle of 20 degrees with the midsagittal plane and perpendicular to the back until bone is reached, usually at a further depth of 3 cm. After aspiration in two planes, 10 cc. of 1 per cent procaine is injected.

parenchyma is not an uncommon complication of the anterior approach technique because the stellate ganglion lies behind the dome of the pleura which shows considerable variation in height. Pneumothorax is seen more commonly in blocks of the right stellate ganglion since the apex of the right lung is 1.5 to 2 cm. higher than that of the left lung and is in very close relationship to the stellate ganglion. The posterior approach to the stellate ganglion offers less risk of penetration of pleura and lung parenchyma. In addition to the dome of the pleura, the brachial plexus, carotid artery, internal jugular vein, inferior thyroid artery and vertebral artery may lie in the path to be traversed by the anterior approach. These structures are avoided in the posterior approach except perhaps for the vertebral artery which shows considerable variation in its relationship to the stellate ganglion (3).

The impunity with which nerve blocks are being performed suggests that the hazards of such procedures are little appreciated. Nerve blocks are not without risk. They demand not merely precise and meticulous technique in their performance but also a proper and rational indication.

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# THE MECHANISM OF STRUCTURAL SCOLIOSIS

## PRELIMINARY REPORT

ALVIN ARKIN, M.D.

An epiphysis may be considered as a endochondral mechanism for producing length. Cartilage columns grow in length, are extruded into the ossifying zone and become part of the shaft. This growth in length is possible against resistance of moderate degree (growth in height despite weight bearing), but it is known from the experiments of Haas (1) that excessive compression will arrest it completely.

It may be considered, also, that sidewise deflection of the growing cartilage columns by oblique forces, will result in growth in an axis oblique to the plane of the epiphyseal line. It is this mechanism which accounts for the slow lateral displacement of slipped femoral epiphysis and torsional displacements and corrections seen, for example, in the growing tibia.

"Idiopathic" scoliosis is a disease of bipeds. It occurs only in the erect spine, and develops and progresses only during the period of epiphyseal growth.

Any erect and elongated jointed column is an unstable structure, in that even minor deviations from the vertical produce compression stresses upon the concave side. These vary directly with the amplitude of deviation and the superincumbent weight.

In a spine which has deviated considerably from the normal because of habitual postural defect or congenital anomaly, muscle imbalance, etc., the compression may reach a degree sufficient to arrest the growth of the epiphysis on the concave side.

It is at this point that the curve becomes structural. The bodies at the apex of the curve become wedged, because of unequal epiphyseal growth, and, acting as wedges under compression, are squeezed out laterally, producing the typical convex side rotation seen in scoliosis. This rotation is both translatory (one vertebrae against the next) and internal, due to internal plastic deformation of the vertebrae by the forces acting upon it.

A contributory mechanism to rotation is the tendency of the posterior soft structures to straighten out under tension, causing deviation of the spinous processes toward the concave side.

Thus the spine, while growing, is doomed by its very plasticity to progression in the direction of the initial displacement, once it exceeds a critical value.

Compensatory functional curves develop in response to the effort to maintain upright posture. The identical factors described above react to convert these into structural curves. Their effect is to diminish the excursion of the first curve from the weight-bearing line; leading to arrest of progression in many cases. It is this mechanism which produces spontaneous arrest in those curves which do not progress because of good compensation. On the other hand an S-shaped

curve may have such marked excursion of the apices from the mid-line, as will cause progression despite perfect compensation.

This plastic deformation of the growing bone is a function of the epiphysis. Thus the same mechanism which produces scoliosis during growth of the main vertebral epiphysis is responsible for adolescent kyphosis at the age when the epiphyseal rings are ossifying.

This mechanism is also the basis of the induced deformities in the bound-foot of chinese girls, the experimental spinal curvatures produced by binding puppies (Wullstein) the increase of flexion in a fused knee in childhood, and the development and correction of bowlegs and knockknees—all examples of arrest or distortion of epiphyseal growth by pressure, and all impossible of production once growth has ceased. It is suggested that all these conditions be classified as pressure induced epiphyseal growth deformations.

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# OBSERVATIONS ON THE EFFECT OF HYALURONIDASE ON URINARY CALCULI

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GORDON D. OPPENHEIMER, M.D.

Approaches to the problem of the dissolution of urinary calculi have been directed mainly at the mineral elements. The most successful results using this method of attack have been reported by Suby and Albright (1) with their "Solution G." Additional methods of dissolving calculi by affecting the crystalloidal components have been used by Higgins (2), Keyser (3), and many others.

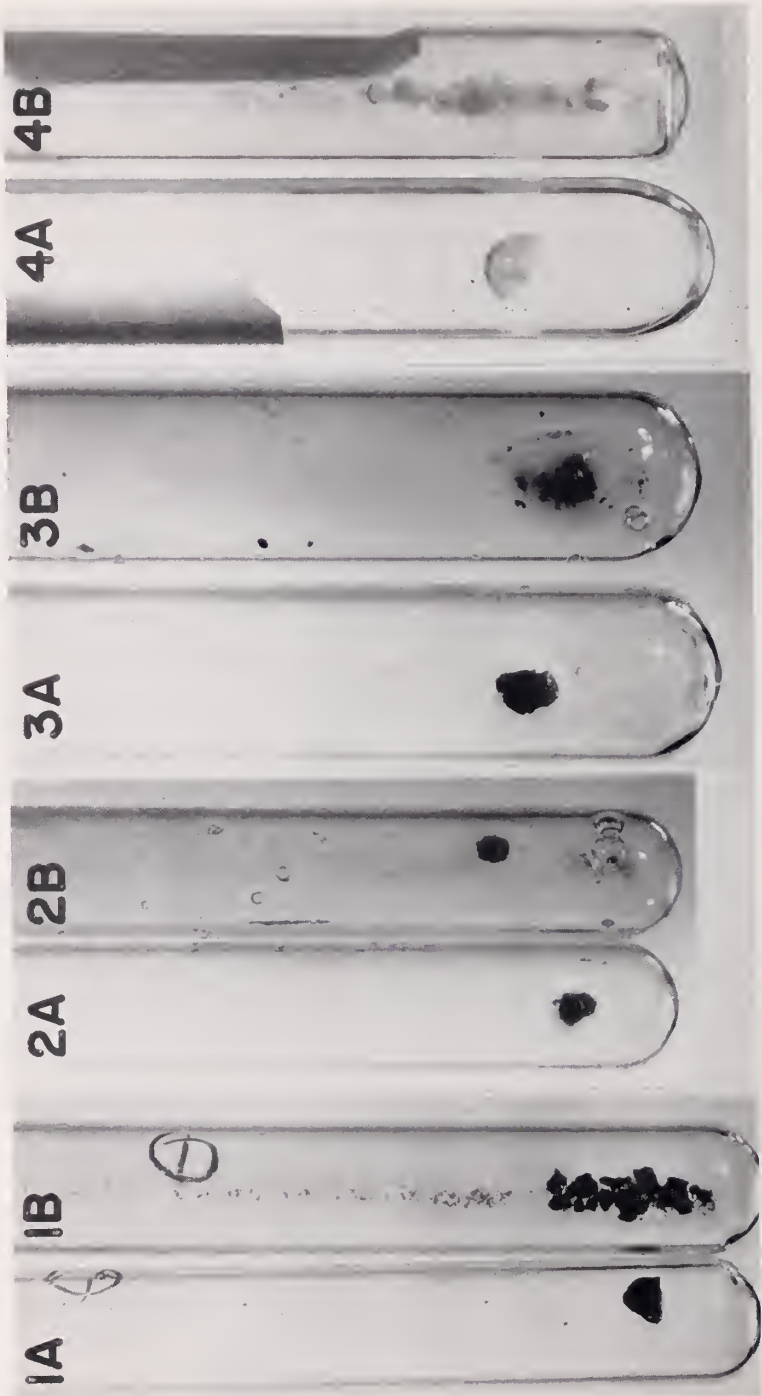
It has been emphasized, however, that in addition to the mineral component of urinary calculi, the colloid or binding matrix is an important physical and chemical constituent of each stone. Lichtwitz analyzed the urinary colloids in 1919 and found that they consisted of a series of complex chemical substances chief among which were nucleic acids, mucin, glycogen, chondroitin sulfate, and a complex polysaccharide containing nitrogen (4). This analysis was repeated in 1942 with similar results by Lindemann and Selvaag (5). According to Joly, the colloid matrix of urinary calculi is derived from the urinary colloids (6). The importance of the colloid binding matrix was further stressed by Keyser (3), who found that only the outer layer of certain calculi could be dissolved by various solutions *in vitro*, after which there remained a gel-like coating. This gel-like coating prevented further dissolution of crystalloid components, and itself remained impervious.

Since attempts to dissolve the mineral constituents have met with only limited success, the need for a colloid matrix solvent which is not injurious to the tissues has been stressed. The aforementioned analyses, indicating that there is a complex polysaccharide containing nitrogen in the colloid binding matrix, suggested that this polysaccharide may be related to the substances now known as hyaluronic acid. It was logical therefore to use hyaluronidase, a hydrolyzing enzyme, in an attempt to dissolve this constituent of the colloid matrix. Furthermore, the chondroitin sulfate present in the matrix may also be hydrolyzed by hyaluronidase preparations (7).

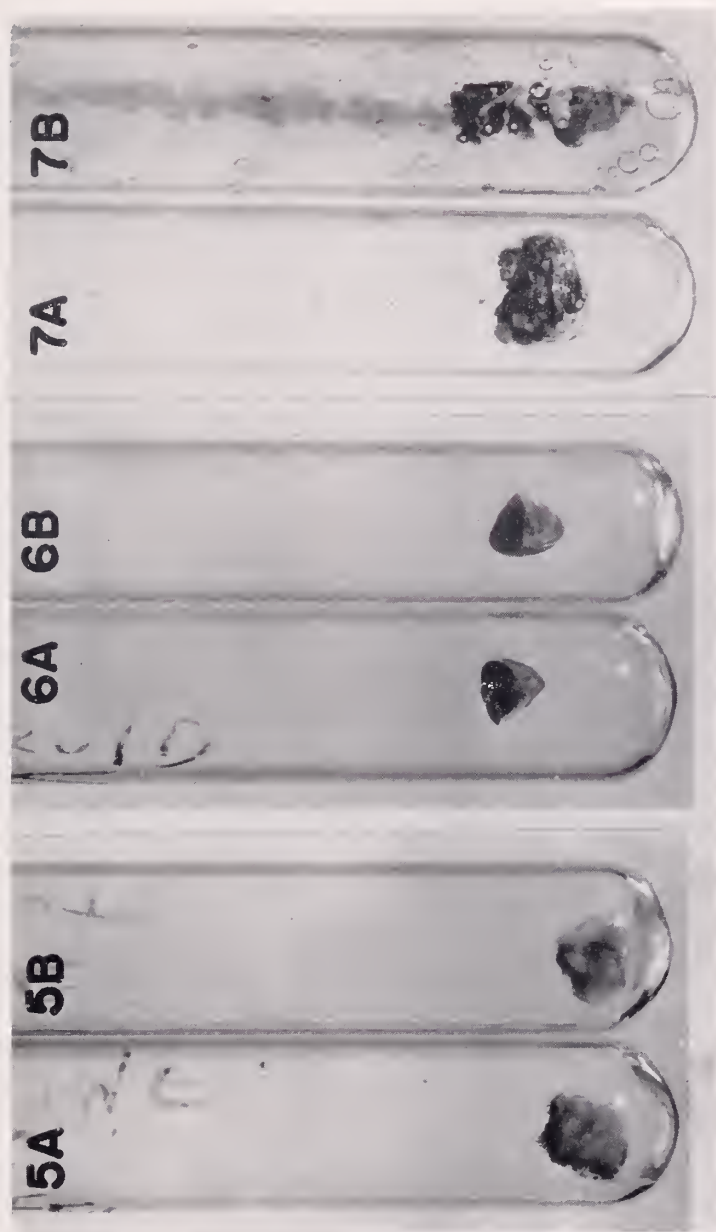
Seven operatively removed urinary calculi were immediately immersed in solutions of Hyronase.<sup>2</sup> Controls were made by placing pieces of the same calculi in normal saline solution and in Suby's "Solution G." Five of the seven test stones showed considerable fragmentation after immersion in hyaluronidase solutions, while the stones in control solutions were unchanged. The maximal effect of the hyaluronidase apparently occurred within the first hour of immersion. The amount of fragmentation is demonstrated in figures 1-7 and tabulated in table I.

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<sup>2</sup> Hyronase is a preparation of bull testis extract with hyaluronidase activity assayed and supplied by Schering Corporation of Bloomfield, N. J.



FIGS. 1A-4B



Figs. 5A 7B

Figs. 1-7. Test tubes labelled A contain stones immersed in saline solution as controls, while portions of the same stones immersed in hyaluronidase solution are labelled B. Numbers of test tubes correspond with stone numbers in table I.



Portions of stone number 1 which had shown fragmentation as indicated in figure 1 were saved for three weeks and were then immersed in a solution of another batch of hyaluronidase. No effect was noted. Another fresh stone (No. 8 in table I) was treated with a new supply of hyaluronidase in normal saline and in Suby's Solution without demonstrable effect.

Local treatments in vivo of a patient with a bladder calculus and another with a large calyceal stone were unsuccessful. However, the bladder in one, and the renal pelvis in the other were irrigated with hyaluronidase solution without apparent clinical ill effect (8).

TABLE I

STONE NO.	MINERAL ANALYSIS	TRU* OF HYALURONIDASE IN 5 C.C. SALINE	FRAGMENTATION OF STONE IN		
			Hyaluronidase	Saline	Suby's solution
1	Calcium carbonate and ammonium urates	2,500	marked	none	
2	Calcium carbonate, ammonium urates, and magnesium ammonium phosphates	1,200	moderate	none	
3	Calcium carbonate and magnesium and ammonium phosphates	250	moderate	none	
4	Ammonium urates and magnesium and ammonium phosphates	4	marked	none	none
5	Magnesium and ammonium phosphates	2,000	none	none	none
6	Ammonium urates and magnesium and ammonium phosphates	500	none	none	none
7	Calcium carbonate, calcium oxalate, and magnesium and ammonium phosphates	1,000	marked	none	none
8	Calcium carbonate	3,000	none	none	none

\* TRU equals Turbidity Reduction Units.

#### SUMMARY

Fragmentation occurred in test tube experiments in five out of eight urinary calculi immersed in a solution of hyaluronidase.

Whether this was a specific effect of hyaluronidase or due to other factors was not definitely determined.

Further observations of the effect of this enzyme on urinary and biliary calculi and on the nature of the colloid matrix of calculi are suggested.

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## ESSAYS ON THE BIOLOGY OF DISEASE

### UREMIA

ELI MOSCHOWITZ, M.D.

The present concept of "uremia" has changed profoundly since its original designation as a symptom complex due to the retention of non-protein nitrogenous substances in the blood, of which urea is the predominant component. It was soon realized that a large moiety of the multiple clinical manifestations of "uremia" were not explainable on such a hypothesis, and for a while attempts were made to derive a toxic substance from the blood which would simulate such symptoms experimentally. Needless to say, such attempts have proven elusive and probably will remain so, for the obvious reason that uremia represents a congregate of clinical phenomena consequent upon a host of factors of which the increase of non-protein nitrogenous products in the blood is only a single, and probably a subsidiary one. As a matter of fact, death never comes from uremia, if one defines uremia in the original sense. Death comes from other factors of which azotemia is only one of the expressions. A person therefore may be said to die *in* uremia but not *of* uremia. Hewlett (1) and his coworkers swallowed 100 Gm. of urea in an aqueous solution over a period of 4 to 6 hours. They experienced headache, dizziness, apathy, drowsiness and fatigue, most marked when the urea concentration in the blood was at its maximum of 150 to 160 mgm. per cent. They had practically no symptoms when the concentration was between 40 and 150 mgm. per cent. A urea content equivalent to about 1 per cent of total body weight is required to cause death in an animal (2), which is far from the maximum ever attained clinically. It is a common experience that urea may be given in doses as high as 100 Gm. daily for weeks to patients for diuretic purposes without any harmful effect. Some supposedly uremic symptoms may even arise in conditions in which there is no increase of these non-protein nitrogenous substances at all. Azotemia and uremia are therefore by no means synonymous. Furthermore, the symptoms and signs of "uremia" do not necessarily correspond to a static change in the organism but represent a biological progression or a summation of a series of altered biochemical and functional organic changes, so that the time element must always be taken into consideration. These altered biochemical and functional organic changes depend largely upon the topography, nature and intensity of the primary disease.

It is fairly well agreed that, aside from protein destruction, an increase in the non-protein nitrogenous substances in the blood is due to diminution in renal function, which is not necessarily due to gross or even microscopic morphological destruction of the organ. The subsequent natural history of the disturbed renal function depends upon the nature of the primary insult. These may be classified into 1. extrarenal diseases or factors, 2. diseases that affect the vascular supply of the organ, 3. diseases that affect exclusively the excretory channels of the kidney, 4. localized renal disease.

1. *Extra renal factors or disorders.* The mechanism whereby renal dysfunction is produced has been aptly called by Fishberg (3) "pre-renal deviation" and he lists the following causes. a. *Severe and protracted vomiting.* Even in the absence of obstruction of the alimentary tract vomiting may cause an increase in the non-protein nitrogen in the blood (4). Such an increase is not always associated with alkalosis, since it is occasionally seen in the cyclic vomiting of children which is accompanied by an acidosis. Its immediate cause is dehydration. Azotemia from any other cause, if accompanied by vomiting, becomes aggravated. b. *In prolonged diarrhea.* Azotemia rarely occurs in adults unless the diarrhea is consequent to a disease of the kidney or the excretory apparatus, and under such conditions, the azotemia is primarily renal in origin. In children, however, azotemia from an uncomplicated diarrhea of toxic origin is often observed (5). Dehydration is probably the immediate cause. c. *Hepatic disease.* Since the liver synthesizes urea, there is usually a diminution in the non-protein nitrogen of the blood in most destructive hepatic disorders. Mann and Magath (6) have shown that in complete hepatectomy the blood urea decreases considerably. Occasionally, however, under certain conditions, azotemia develops. Myer and his colleagues (7) in a series of 180 cases of hepatic disease with jaundice found a moderate increase of non-protein nitrogen in the blood in 39 per cent and a high increase (over 70 mgm. per cent) in 10 per cent. This was observed in such maladies as hepatitis, cirrhosis, benign obstruction and in malignant diseases. They found that the increase is due to an associated dysfunction of the kidney and not to an increased breakdown of protein. The prognosis paralleled the degree of azotemia. Another form of the "hepatic-renal syndrome" is the so-called "liver death" following operations on the gall bladder which is accompanied by an azotemia. Keating, Bower and Priestley (8) ascribe certain of these fatalities to a cholorrhea which results in a profound loss of chloride. The cholorrhea usually follows operations for cholelithiasis and is characterized by the passage of large quantities of bile, circulatory collapse, dehydration and a profound hypochloremia. Dramatic recovery follows the infusion of sodium chloride solution. d. *In diabetes.* Azotemia may arise in the comatose stage independent of any associated renal lesion. It usually arises in individuals who have had an unusual protracted ketosis and who become oliguric or even anuric. It is associated with marked dehydration and is usually reversible by intravenous saline glucose and insulin. e. *In the crisis of Addison's disease.* The cause of the azotemia in Addisonian crisis is not entirely clear, but there is evidence that even in the compensated phase of the disease there is some disturbance in renal function. In 10 patients Talbott and his coworkers (9) found disturbances of the rate of absorption of glomerular filtrate and tubular reabsorption capacity for glucose. Renal plasma flow and tubular capacity for excreting diodrast were less affected. Administration of desoxycorticosterone acetate partially corrected, but only temporarily, these deficiencies. Inasmuch as no structural changes were found in their fatal cases, they assume that these disturbances were "functional" in nature. They speculate on the cause, but

they do not believe that hypotension can explain their findings. f. In *traumatic and post operative shock*. In the shock following extensive burns, after coronary thrombosis, and in acute pancreatitis, azotemia may be severe. It usually is associated with marked oliguria or anuria and the specific gravity of the urine is often low (3) showing that the kidney may lose its concentrating ability in the course of but a few days. The immediate cause of the dysfunction is presumably due to diminished renal blood flow (3). In most cases it is responsive to blood transfusion. g. A moderate transitory degree of azotemia has been reported in large *hemorrhages into the intestinal tract*, even without shock: in such instances, the azotemia has been ascribed to the increased nitrogen intake from the absorbed blood. Johnson (10) in a well conducted study reports that after a single massive hemorrhage the azotemia may disappear in three days. He found that a marked rise of non-protein nitrogen and urea in the blood only arises in patients in whom there is a reduction in renal function as determined by the urea clearance and creatinine clearance tests. There was no change in the serum chloride or  $\text{CO}_2$  combining power. After the administration of 1200 to 1500 cc. of citrated blood he found only transient and slight rises in patients who had normal renal function, but higher and more prolonged rises in those whose urea clearance test was half the normal. The absence of azotemia in certain patients after a severe gastrointestinal hemorrhage may be accounted for by this observation. Corcoran and Page (11) found experimentally that bleeding caused a decrease in renal blood flow through the mechanism of hypotension. The glomerular filtration rate is disproportionately decreased. After transfusion this is restored and is accompanied by an increase in the flow of urine. The probability is strong that in some patients a sufficient grade of shock had been present before the patient came to observation, in order to produce a temporary dysfunction of the kidneys. Indeed Alsted (12) found impaired renal function in his series, but only in those that were accompanied by shock. The azotemia of hemorrhage has no relation to anemia because it disappears even before there is any rise in hemoglobin or red blood cells (4). h. In various *acute infections*, azotemia may attain an appreciable degree, especially in pneumonia, and the degree is deemed of value in prognosis. When azotemia is present it is usually accompanied by oliguria. Obviously, an azotemia may arise from a complicating nephritis or cardiac failure, but it occurs even without any gross evidence of such complications. In such instances, the azotemia has been ascribed to increased protein destruction. Inasmuch as renal functional tests are usually not feasible in such grave disorders, we do not know whether renal insufficiency is responsible. Obviously, if vomiting intervenes the azotemia is increased. i. In the *terminal phases of right heart failure*, for instance in rheumatic mitral disease, azotemia of considerable degree, even 100 mgm. per cent, may arise. It is always accompanied by a marked oliguria. When azotemia occurs, the previously good concentration of the urine becomes comparatively low in comparison to the volume of urine passed, as Fishberg (3) has pointed out. Indeed, he regards this phenomenon as invariable in all types of pre-renal azotemia, and it can only be interpreted as an evidence of

renal insufficiency. In the heart failure of hypertensive diseases, the azotemia when it arises, is exaggerated by anatomical renal damage consequent to vascular disease. j. *Pyloric and intestinal obstruction*. A high grade of azotemia is notorious in either pyloric or intestinal obstruction, and the higher the obstruction the greater the azotemia. Furthermore, this occurs even before vomiting sets in and is observable even in obstruction of the cardia when vomiting cannot occur. There are a number of factors that may give rise to the azotemia. Definite evidences of renal insufficiency have been demonstrated in the human being (13) and in experimental obstruction (14). On the other hand Haden and Orr (15) have shown experimentally, by comparing the total nitrogen excretion with the non-protein nitrogen in the blood, that in upper gastro-intestinal tract obstruction there is a marked protein destruction. Whether due to starvation or to a toxic factor they cannot say. The azotemia has been viewed by some as the consequence of chloride loss because it can be mitigated to a certain extent by the intravenous administration of saline. That chloride loss cannot be the entire cause is proven by the fact that some grade of azotemia usually persists. The beneficial effect of the saline is more likely the consequence of its diuretic effect. k. In *gout*, especially during the acute febrile episodes, there may be a moderate azotemia. The azotemia is related to disturbances in renal function, especially in individuals in the senescent years, when hypertension and vascular disturbances are frequently associated.

These azotemias of extrarenal origin are associated with other and sometimes profound chemical and organic functional changes. In most there is lowered chloride content of the blood, and especially of the sodium content, due to loss from one route or another. There is usually a high carbon dioxide combining power in the blood with resulting alkalosis. The only exceptions to this are in diabetes (due to retained ketone bodies), and in Addisonian crises (due to retained phosphates and sulfates); under such conditions there is acidosis, which explains the hyperpnoea so often noted in these maladies. In alkalosis, the most prominent symptom is tetany, which is occasionally observed in pre-renal azotemia, especially in those states that are accompanied by prolonged vomiting. Dehydration is common and is evidenced by a loose dry skin, and in extreme cases, as in diabetic coma, by softening of the eye ball. Dehydration is also reflected in a cyanosis, due to hemoconcentration. In conditions associated with shock, the circulating blood volume is decreased, the peripheral vessels are contracted and peripheral circulatory failure results (3). It is not always easy to assign a symptom or sign to this or that chemical or organic functional change. Moreover, there is a strong likelihood that these clinical phenomena are the results of a combination or summation of these changes. The difficulty is further enhanced by the fact that the underlying disease, whether it be due to a toxin or an infection, a mechanical disturbance or a metabolic disorder, brings in its train a host of clinical phenomena which complicate the picture. But even divorcing the latter factors, it is clear that the symptoms and signs of pre-renal azotemia vary according to the underlying disease, and that the term "uremia" must be applied with much elasticity in order to classify these disor-



ders. If one so desires, one might apply the term "asthenic uremia" (16) to this group. The difference between this type and that accompanying renal disorders will be emphasized in the following sections.

In most of these disorders, as Fishberg (3) emphasizes, hypotension with consequent diminution in renal blood flow is an important mechanism in the production of the azotemia.

2. *Diseases that affect the vascular supply of the organ.* These diseases differ from the conditions we have previously discussed by the fact that the clinical expression is modified profoundly by the associated hypertension. In acute glomerulonephritis, which is generally viewed as the localized expression of a generalized capillary disease, azotemia may arise, especially if there is oliguria and particularly if there is anuria. The azotemia may attain considerable heights. Nevertheless death from "uremia" is rare. In practically all reports, the diagnosis of "uremia" is based on clear evidences of either hypertensive encephalopathy, retinitis or left ventricular failure, conditions entirely dependent upon the associated persistent hypertension. Such evidences of "uremia" may even subside spontaneously or by appropriate treatment. In the "malignant phases" of glomerulonephritis, the same conditions hold, except that the "uremic" manifestations are usually terminal.

In exceptional instances a chronic glomerular nephritis runs its course without the usual hypertension. In such instances, anuria or a profound oliguria may be terminal and death with profound azotemia ensues, but without evidences of hypertensive encephalopathy, retinitis or left ventricular failure. The manner of death is similar to that which, as we shall describe subsequently, follows bilateral obstruction of the ureters.

In renal disease following long continued essential hypertension, and in which the dysfunction is largely conditioned by vascular disease, the so-called clinical manifestations of "uremia" differ sharply from the azotemia that have been previously described. This is particularly evident in "malignant nephrosclerosis." Most individuals with essential hypertension do not reach this stage, because they usually die before this event either of cardiac failure or a vascular accident. In "malignant nephrosclerosis," azotemia is usually a terminal event and with few exceptions, is irreversible. But some of the supposed "uremic" manifestations, for instance the retinitis, hypertensive encephalopathy and left ventricular failure, bear no relation whatever to the degree of azotemia. These signs are entirely sequential to the concomitant hypertension, the proof being that they only arise in hypertensive states with or without azotemia. A renal malady unaccompanied by hypertension, no matter how aggravated the evidences of renal dysfunction may be, never develops hypertensive encephalopathy. We (17) have tried to show that hypertensive encephalopathy is associated not only with a high diastolic pressure, but with one that has been persistent for a protracted period. It is always associated with a high pressure in the cerebrospinal fluid, which is consequent to two factors: 1. an increased permeability of the hematoencephalic barrier, and 2. a persistent high venous pressure. The papilledema, which is viewed by some as peculiar to

"uremia," is a late result of these two factors. The only sign in malignant nephrosclerosis that is directly dependent on azotemia and to no other factor is the so called "uremic frost." It is unlikely that azotemia alone is responsible for the pericarditis of "uremia" because in experimental animals in whom enormous non-protein nitrogen figures in the blood can be attained by various methods, a pericarditis is never seen. As far as my experience goes, this type of pericarditis is seen only in azotemia consequent to vascular renal lesions. Its pathogenesis is unknown. The "uremic" enteritis also bears no relation to the degree of azotemia. Jaffe and Loring (18) submit strong morphological evidence that localized mucosal hemorrhages and vascular lesions are primarily responsible. Hemorrhagic lesions of the mucosa of the intestine can be produced experimentally by bilateral nephrectomy or bilateral ureteral ligation (19).

3. *Obstruction of the renal excretory apparatus.* Clinically, this follows bilateral ureteral obstruction or narrowing by destructive lesions of the renal pelvis, in prostatism, in sulfanilamide poisoning and in post-transfusion reactions. Anuria arising from bilateral ureteral obstruction, either by calculi or by neoplastic invasion, causes a rapid and progressive azotemia, especially of the urea component. The plasma chloride at first mounts rapidly, but later sinks, even to below normal, due to salt deprivation and especially to vomiting, which usually sets in early. The blood pressure remains normal but after some days rises but only to moderate heights. Moderate hypertension also follows experimentally after bilateral ureteral ligation, (19) (20) probably by the mechanism of ischemia. On the other hand after bilateral nephrectomy, no elevation of blood pressure occurs. The azotemia is accompanied by marked rises in blood phosphates and sulphates, causing an acidosis, which however is soon neutralized by loss of salt. Especially interesting and noteworthy is a pronounced rise in potassium (21-24) in animals in whom bilateral ureteral ligation or bilateral nephrectomy has been performed. Hoff, Smith and Mukler (21) noted electrocardiographic findings characterized by an absence of P waves (which was not due to auricular fibrillation), changes in the T waves and widening of the Q R S complex. These changes were noted only when a certain potassium blood elevation was attained, and corresponded to those obtained by injecting large doses of potassium intravenously. The animals died with cardiac arrest, respiration continuing for a short while after the heart ceased to beat. At autopsy the heart was found in diastole. Since then, the identical chemical and electrocardiographic changes have been observed by Bywaters (25) in crush muscle injuries following blitz bombing and by Fitch and Marchand (26) in two cases of nephritis. Under ordinary clinical circumstances, blood potassium levels never attain the heights necessary to produce these electrocardiographic changes, because potassium is easily excreted. At all events, death in the experimental animals was correlated with a certain increase in the blood potassium level rather than to the degree of azotemia (21). The clinical expression following bilateral ureteral closure differs profoundly from that observed in vascular disease. It is best observed in cases of closure of the ureters by neoplasm or in sulfanilamide poisoning, whether the latter is due to crystallization in the urinary



passages or as in sulfathiazole poisoning, when no crystallization is found. For some days, the patient feels remarkably well. Later there is drowsiness and headache. Only terminally, do vomiting, muscular twitchings, occasionally diarrhea and a moderate elevation of blood pressure develop. Death comes after a short period of coma. Sometimes it occurs suddenly, as in experimental animals and in the cases reported by Bywaters (25) and Fitch and Marchand, (26) presumably from potassium intoxication. I have observed a patient with complete anuria for a period of eighteen days consequent to neoplasm, who aside from headache felt well up to within 24 hours of death, when coma set in. Myers (27) observed a patient under similar circumstances who lived 30 days. These patients never suffer from hyperpnoea because the primary acidosis is neutralized by loss of base. Because the hypertension is only a terminal phenomenon and never exaggerated, hypertensive encephalopathy, retinitis and left cardiac failure never arise. Similar clinical phenomena occur in post transfusion reactions (28).

The clinical picture following partial occlusion of both ureters cannot be portrayed because published reports are few in number and not sufficiently well studied. One would surmise that it would depend largely upon the degree and duration of occlusion. Experimentally, Winternitz and his coworkers (19) by compression of both ureters in dogs with Goldblatt clamps found that there was an irregular rise in non-protein nitrogen and an inconsistent rise in blood pressure sometimes attaining 80 mm. Hg above the normal. The animals survived between 7 and 55 days after the procedure. Winternitz and his coworkers were interested in the anatomical changes and further data are not available.

The commonest cause of renal dysfunction due to obstruction of the renal excretory apparatus is prostatism. This is only observed in neglected cases, when the bladder remains distended and back pressure has caused hydronephrosis. An azotemia sometimes of considerable degree may arise; this is usually accompanied by a rise of blood pressure. Both the azotemia and the hypertension drop sharply after adequate drainage of the bladder is instituted. As a consequence, death from "uremia" as the result of prostatic obstruction today is much less frequent than formerly.

4. *Uremia in localized renal disease.* Most of these disorders belong to the group of "surgical kidneys" and include hydronephrosis, chronic pyonephrosis or pyelonephritis, renal tuberculosis and neoplasms. To these we may add multiple cystic disease of the kidney and bichloride poisoning. Inasmuch as the compensatory capacity of the kidneys is great, it necessitates considerable destruction and over a prolonged period before azotemia arises. Unilateral nephrectomy as a rule does not give rise to an azotemia, except perhaps a transient post-operative one, so that a consistent rise in non-protein nitrogen in the blood after unilateral nephrectomy is strong presumptive evidence that the remaining kidney is affected. Nearly three quarters of the total bilateral renal content may be removed with survival of the animal (29, 30). Under such circumstances there is a temporary rise of non-protein nitrogen which soon recedes

to normal, probably due to compensatory hypertrophy, and it remains so if the animal is kept on a diet not too rich in protein.

Although the above mentioned disorders imply a greater or lesser destruction of the renal parenchyma, the degree of kidney dysfunction that may be associated is not necessarily proportionate to the degree of destruction, because of compensatory adjustments. Furthermore, it depends upon whether the vascular supply of the organ has been diminished by either compression or destruction and whether one or both ureters have been occluded. When, therefore, in the course of these maladies, azotemia develops, the clinical expression of the resulting "uremia" will be modified by whether one or the other of these two factors or both are associated. We will discuss these maladies in order.

a. *Hydronephrosis*. A unilateral hydronephrosis with the remaining kidney intact, rarely, if ever, leads to an azotemia. If however, the hydronephrosis is of long standing, fibrosis and contraction may occur with resulting hypertension, which in turn may in time give rise to an azotemia. Individuals with bilateral hydronephrosis are specially subject to hypertension, sometimes to an extraordinary degree (31). Under such circumstances, an azotemia may be accompanied by hypertensive encephalopathy, retinitis and left ventricular failure.

b. *Chronic pyelonephrosis or pyelonephritis*. These two lesions are grouped together because they are morphologically nearly always associated. They are especially common in females and arise from either a pyelitis from pregnancy or in childhood. Aside from a persistent pyuria and a progressive lowering in renal concentration the early course is usually silent. Eventually an azotemia supervenes which is symptomless for many years. Longcope (32) observed one patient who had a persistent azotemia of 70 mgm. per cent over a period of four years. In the terminal phases hypertension develops with its consequences. In a fair proportion, hypertension never develops. The latter succumb as do individuals with bilateral ureteral obstruction. As in hydronephrosis, the intensity of the process depends upon whether the disease is unilateral or bilateral. There have been a number of reports of cure by nephrectomy of hypertension due to unilateral pyelonephritis (33).

c. *Tuberculosis*. We do not refer to the albuminuria that occasionally arises in the course of pulmonary tuberculosis. This is usually not associated with much renal dysfunction. The degree of azotemia caused by tuberculosis of the kidney proper depends on whether the process is bilateral or whether it is associated with a hydronephrosis from ureteral involvement, or whether amyloidosis with contraction has occurred. Contraction of the organ with fibrosis even without the intermediacy of amyloid changes may even occur (31). Rarely, a glomerulonephritis may be a complication. With contraction hypertension may arise, but it rarely attains considerable levels, because of the attendant weight loss and general weakness. Death only exceptionally occurs in "uremia." Usually the cause of death is either pulmonary or miliary tuberculosis, cachexia or amyloidosis.

d. *Cystic disease of the kidney*. Polycystic kidneys are congenital and nearly always bilateral. They vary in the degree of the destructive process so that they may be symptom-

less and are often only discovered in routine examinations or at post-mortem. Clinical manifestations usually arise in the later years. Statistics on the incidence of azotemia or hypertension are necessarily only approximate because the time factor is not taken into consideration. Thus Oppenheimer (34) who studied a large series found that hypertension occurs in 57 per cent and a urea blood nitrogen of 50 mgm. per cent or more in 75 per cent, and a blood urea of 100 mgm. per cent or more in about a third of the total. The probability is very strong that more prolonged observation would raise the incidence. The high incidence of hypertension in polycystic kidneys is no doubt due to ischemia from destruction or obstruction of the blood supply (35, 31). The blood pressure may terminally attain heights comparable to those observed in malignant nephrosclerosis. In the intermediary phases of the disease, the patients feel comparatively well. I have on a number of occasions witnessed over a period of years individuals who showed 60 mgm. per cent blood urea and over, and who were ambulatory and in fair health. The manner of death depends on the degree and duration of the hypertension. If the hypertension is high and of long standing, retinitis, encephalopathy and left ventricular failure may complicate the terminal picture of "uremia." If hypertension is absent or moderate, the patients die as if they had bilateral ureteral obstruction. e. *Neoplasms of the kidney*. Non-malignant neoplasms rarely cause any serious renal dysfunction. The occurrence of azotemia in malignant neoplasms of the kidney depends not only on the degree of the destructive process but also upon whether a hydro-nephrosis has been engendered. This occurs in about 20 per cent, according to Kududschanow (36). It also depends upon whether degenerative and fibrotic changes within the parenchyma arise, due to pressure by the neoplasm. The age of the individual undoubtedly contributes because of the common vascular disease and hypertension incident to senescence. At all events, an azotemia of any degree is exceptional, because the ravages of the disease cause death before any significant azotemia develops. f. *Acute mercury poisoning*. The dominant action of mercury is on the tubules causing destruction and necrosis. The glomeruli show congestion, with occasional exudation into the glomerular capsule (37). Depending on the size of the dose, oliguria followed by anuria occurs somewhere between the fourth and tenth day (38). This is followed by an intense azotemia, a marked lowering of the blood chloride, and a lowering of the alkali reserve with a resulting acidosis, the cause of which is not clear. Howard (38) believes it is dependant on a disturbance of the ketone metabolism (K poisoning?). He has even noted dyspnoea in the terminal phases. The patients die like those with bilateral ureteral obstruction. Indeed Hayman and Priestley (39) remark on the close resemblance of the blood changes to those observed in experimental bilateral ureteral ligation.

It may be of interest in relation to the subject of azotemia in pure renal involvement that Winternitz and his coworkers found (40) that animals after bilateral nephrectomy live nearly twice as long as those after bilateral ureteral ligation. The reason for this is not clear, but it certainly is not due to the azo-

temia, since it bore no relation to the degree of the non-protein nitrogen levels in the blood.

#### SUMMARY

It is apparent therefore that of the wide variety of symptoms and signs that have been ascribed to "uremia" in the past, azotemia itself contributes very little to the sum total. The only symptoms that may be ascribed to the azotemia are headache, somnolence, the gastro-intestinal symptoms and the uremic frost on the skin. The remainder are in part the consequence of factors independent of the azotemia, notably the hypertension, the electrolytic disturbances of sometimes totally different patterns, the acidosis or alkalosis, the dehydration, the phenol and potassium intoxications and the diverse dysfunction of one or other parenchymatous and endocrine organs. Such tests as the xantho-protein test, supposedly for phenols, which Belcher devised to distinguish asthenic from the hypersthenic type of uremia loses much of its significance. The term "uremia" is compounded of a host of different and often opposing factors, and any attempt at a unifying concept is doomed to failure. For future study on "uremia" it would serve a more useful purpose to try to correlate clinical phenomena in terms of changes in the organism to a particular disease and not to such an abstract concept as "uremia." As a symptom complex, the term "uremia" is as obsolete as the terms "fever" or "headache."

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## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Periarteritis Nodosa with Involvement of the Choroidal and Retinal Arteries.* J. GOLDSMITH. Am. J. Ophth., 29: 435, April, 1946.

A case of Periarteritis Nodosa involving the eye is reported with necropsy findings. This syndrome is diagnosed for the first time intra vitam by ophthalmoscopic observation in conjunction with the physical findings and the clinical course. An aneurysmal dilatation of the fusiform type is observed in the fundus of the right eye, involving the inferior temporal artery. Other ocular manifestations of periarteritis nodosa are briefly reviewed. The possibility of inducing hyperergic states within the human body by sulfonamides and sera administration is discussed. The patient in this report who had received five courses of sulfonamides (a total of 232 Gm.), over a period of four months might well fit into this category.

*Aqueous Fibrin Fixation of Corneal Transplants in the Rabbit.* H. M. KATZIN. Arch. Ophth., 35: 415, April, 1946.

Corneal grafts were performed in rabbits, using the fibrin formed in the anterior chamber as the only fixing agent. The technic used is described, and the procedure was performed in 37 eyes. The grafts held in 86 per cent and remained clear in 48 per cent of the eyes. The author hopes soon to be able to use fibrin in a similar manner in operations on the human eye. He believes that there is great significance in the successful use of fibrin to hold corneal grafts in place during healing. The significance is great not only because the operation itself may be vastly simplified thereby but because the corneal graft is an ideal test medium for wound healing of all types. The area of contact between graft and host, after the anterior chamber has reformed, is of very small dimensions. Also, the tissue reaction to the fixing agent is immediately apparent in the transparency of the corneal graft.

*Sequelae Following Oral and Topical Use of Penicillin.* L. KLEINFELD. New York State J. Med., 46: 8, April, 1946.

Following the oral or topical use of penicillin, we have observed some unpleasant sequelae. One, abdominal cramps and distention after the ingestion of penicillin. Two, the occurrence of ulcerative lesions in the mouth while using penicillin lozenges. This also was noted following the ingestion of penicillin tablets. Three, dermatitis around the nares while using penicillin ointment in the nostrils. Although some of the symptoms could be ascribed to the substances with which the penicillin was mixed, the most likely etiological factor seems to be the penicillin itself. Case reports are given.

*Papilloma of the Gall Bladder.* D. MILLER. New England J. Med., 234: 473, April, 1946.

Papilloma of the gall bladder occurs infrequently but can be diagnosed by roentgenological examination preoperatively. The correct preoperative diagnosis was made, in this way, in 3 consecutive cases operated by Dr. Ralph Colp. The symptoms which bring the patient under observation are those usually associated with chronic cholecystitis. The papillomas, often multiple, are found either with or without gall stones. They vary in size from 1 to 2 mm to 1 cm in length and are usually delicate filamentous structures. Cases of gall bladder exhibiting both carcinomas and papillomas have been described in the litera-



ture. The transition from benign to malignant change has not been seen. Cholecystectomy relieves the patients' symptoms.

*The Treatment of Bacillus Proteus Infections with NU-445.* S. J. SARNOFF, M. A. FREEDMAN AND A. A. HYMAN. J. Urol., 55: 417, April, 1946.

Fourteen cases of *Bacillus proteus* infection of the urinary tract, and 1 case of local infection of the eye socket have been presented. Eleven cases were apparently favorably influenced by therapy with Nu-445, and in 9, bacteriological reversals consisting of three successive negative cultures, were obtained. Suggestions for the improvement of therapy are set forth. The preliminary nature of these data is emphasized, and it is realized that this study is not sufficiently extensive to establish a curative effect. However, it is felt that a modification of the course of the disease is obtainable in the majority of cases.

*The Problem of Primary Lateral Sclerosis.* I. S. WECHSLER AND S. BRODY. J.A.M.A., 130: 1195, April, 1946.

Based on a study of 15 patients followed for a great many years, culled from 60 patients with the same diagnosis, the authors conclude that primary lateral sclerosis seems to be a distinct clinical syndrome unrelated to other scleroses. The condition of the patients remained unchanged. The words sclerosis and degenerative are descriptive terms of pathological end processes and tell nothing of etiology or of pathogenesis. It is not known whether they represent virus infections, deficiency reactions or allergic syndromes. They appear to be the result of the selective affinity of various endogenous or exogenous noxious agents for the nervous system. For the present the various entities must be viewed merely as the clinical expression of anatomicopathologic syndromes of unknown etiology and pathogenesis. Neither multiple sclerosis nor amyotrophic lateral sclerosis presents a single etiologic or pathologic entity. Each consists of several different syndromes, although clinically they fall into fairly consistent groups. Amyotrophic lateral sclerosis consists of two large groups, namely the primary and symptomatic, the latter of at least three subdivisions. There seems to be an increase in the incidence of the lateral and other scleroses, that is, of the so-called degenerative diseases of the nervous system. There also appears to be an increase in the more benign types, so that, despite want of knowledge of causes, one may venture a less hopeless prognosis.

*Combined Penicillin and Hydrogen Peroxide Aerosol Therapy in Lung Infections.* H. A. ABRAMSON. Ann. Allergy., 4: 199, May, 1946.

Hydrogen peroxide solution, plus 10 per cent glycerol in physiological saline, may be readily nebulized without loss of stability, whether used as hydrogen peroxide directly or as urea peroxide. These solutions may be administered to both animals and man in germicidal concentrations without appreciable irritation. Preliminary data on animals indicate that even when hydrogen peroxide aerosols of the type described are administered over prolonged periods, neither the lungs nor the eyes are damaged. A brief report is made on the effect of administering hydrogen peroxide (urea peroxide) aerosols in cases of asthma, asthma complicated by infectious bronchitis and bronchiectasis with lung abscess. In these cases, not only was hydrogen peroxide (urea peroxide) aerosol used alone, but it was also combined alternately with penicillin aerosol. The use of combined penicillin and hydrogen peroxide aerosols provides a method of approach to the destruction of both Gram-positive and Gram-negative organisms with readily available antibiotic material. A program is outlined in which combined penicillin and urea peroxide aerosol therapy, as described in the foregoing, is being applied to retard primary and secondary infections in pulmonary tuberculosis.

## BOOK REVIEW

MODERN TREATMENT OF PEPTIC ULCER. ASHER WINKELSTEIN. New York, Oxford Medical Publication, 1948, 205 pp.

This book, as might be expected, coming from one who has made so many valuable contributions himself, is an excellent summary of the subject. It is naturally weighted with his own experience and opinions and lays the greatest stress on the author's really great contribution, the intragastric drip therapy.

Because of the inclusion of the narrative from the author's sound-color motion picture "Intragastric Drip Therapy" and a chapter from his previous book "Outline of Gastro-intestinal Diseases" there occurs some unavoidable repetition in the text.

In his discussion of the important question of the psychosomatic relationship in peptic ulcer, the author presents, surprisingly enough, not only the pros but the cons of this theory. He finally concludes that peptic ulcer probably is, in most instances, a psychosomatic disease.

Also, on the subject of vagotomy, in the development of which the author has played a pioneer role, he concludes that vagotomy is a valuable adjunct in the surgical therapy of peptic ulcer. However, he advocates it, not as a sole procedure, but in combination with partial resection. Winkelstein is rightly careful in not giving the final answers since the leaders in the profession are still very much divided in their opinions on these two questions.

The chief value of the book lies in the fact that the author, after 25 years as Chief of the Gastro-intestinal Clinic at The Mount Sinai Hospital, has given to the medical profession his carefully considered opinion on the controversial aspects of the peptic ulcer problem.

Of additional value is the inclusion of the entire chapter on Peptic Ulcer from the author's "Outline of Gastro-intestinal Diseases." Since this contains in concise form the complications of ulcer and their treatment as well as the dietetic and drug therapy of uncomplicated peptic ulcer, it should prove of great value to the general practitioner.

In view of the timely discussions of the intragastric drip therapy, vagotomy, entero-gastrone, Co Tui therapy, the psychosomatic relationship, and the prophylaxis of peptic ulcer, this book should properly find its place in the hands of medical students, practitioners and, of course, specialists in this field.

## NEWS AND NOTES

### THE MOUNT SINAI HOSPITAL ELECTS PRESIDENT AND PRESIDENT EMERITUS

Alfred L. Rose became the fourteenth President of the ninety-six year old Mount Sinai Hospital following his election at the annual meeting of the Board of Trustees of that institution last evening. George B. Bernheim, who wished to retire from the office he has filled since 1945, was elected President Emeritus, the second to be chosen for that office in the Hospital's history. Joseph Klingenstein, Vice-President, was reelected and three new Vice-Presidents, Richard Goldsmith, Leo Gottlieb and Charles A. Riegelman were named. Joseph F. Cullman, Jr., Treasurer, and Ira A. Schur, Associate Treasurer, were reelected and Carl H. Pforzheimer, Jr. was elected Secretary, resuming the office he vacated in 1943 to enter the military service.

The new President has been a Trustee of The Mount Sinai Hospital since 1933, President of The Mount Sinai Hospital School of Nursing since 1943, and a Vice-President of the Hospital since 1945. He has also been a trustee of the Federation for the Support of Jewish Philanthropies for many years.

Born in New York City, Mr. Rose attended Public School #87 and Horace Mann High School; was graduated from Princeton University in 1908 and from the New York Law School in 1910. He has practiced law since his admittance to the bar in 1911 and is a member of the firm of Proskauer, Rose, Goetz and Mendelsohn. He is a director of a number of corporations. He served in the U. S. Navy in World War I as a line officer on the battleship U.S.S. Wisconsin with the Atlantic fleet.

Mr. Bernheim, President Emeritus, has been a Trustee of the Hospital since 1923, was Vice-President from 1938 to 1945 when he became President. Born in New York City, he attended Dr. Sachs School for Boys and was graduated from Columbia University School of Mines in 1901 and is President of R. Neumann & Co., tanners, of Hoboken, N. J. He is also a trustee for the Federation for the Support of Jewish Philanthropies.

### NEW PROFESSIONAL TRAINING OPPORTUNITIES OFFERED ARMY DOCTORS

A revised and greatly expanded professional training program for regular Army and Reserve Medical Officers was announced today by Major General Raymond W. Bliss, Surgeon General of the Army. In line with the policy of providing in the U. S. Army the highest standard of medical care in the world, the program calls for 1900 new doctors in the Regular Army and an increasing number of volunteer Reserve officers on active duty. The program is designed to give many more Army doctors the training needed to meet the requirements for certification by the American Specialty Boards, and to further integrate civilian and military medicine. The new program will facilitate the classification and career management system already in practice in the Medical Corps whereby every effort is made to assign professional officers to posts where they can practice in their special fields of interest.

Five major aspects of the new training program were described by the Surgeon General:

(1) Physicians already resident in civilian hospitals are now eligible for commissions in the Regular Army. Those commissioned may continue their residencies with full pay and allowances from the Army and will be assigned by the Army to the civilian hospital in which they are already resident. Even in the event of a major emergency, residents will complete their training, if it is at all possible. Chances of continuing training for these men will be at least as good as those of civilian doctors in resident training. The Surgeon General's Office will commission 300 residents under this aspect of the program in 1948, 300 in 1949-50 as senior residents, 100 as residents and 150 as junior residents.

(2) Civilian interns are now eligible for Army Medical Corps Reserve commissions, and may continue their internship with full Army pay and allowances. Those so commissioned will undertake to accept a commission in the Regular Army on completion of their internship, and will then be permitted to compete for Army residencies in either Army or civilian hospitals. In 1948 and again in 1949, 300 interns will be included in this phase of the training program.

(3) During 1948, 500 younger doctors will be commissioned and assigned to duty at army hospitals in order to compete for 260 residencies in both army and civilian hospitals. Competitive examinations will begin either in September or October 1948. These residencies are apportioned among the various specialties according to the needs of the Army Medical Corps. Resignation of officers commissioned under this phase of the program will not be accepted within one year after the date of commission.

(4) One hundred and fifty commissions in the grades of major, lieutenant colonel and colonel will be offered in 1948 and another 150 in 1949, to doctors who have completed their training. This aspect of the program is not limited to those men already certified as specialists, since outstanding officers for command and staff positions are needed as well as professional men. Applicants for these commissions in higher grades will not be considered for residencies or specialty training.

(5) Active Reserve Service for specific positions and limited periods will be offered doctors who are not interested in a regular Army career. General announcements for such vacancies, will be made from time to time. Those who come into the service in this manner will not be eligible for residencies, but time spent in practice under this aspect of the program may receive recognition by the specialty boards.

The program is designed to attract to a regular Army career medical talent of the highest caliber. One year of active duty as distinguished from training duty is expected for each year of training, whether the training is received in army or civilian institutions. Resignations will not be considered until this obligation has been fulfilled.

Training continuous until completion of the requirements for Specialty Board certification is a definite aim of the program, the Surgeon General emphasized.

The program has been presented to the Council on Medical Education and Hospitals of the American Medical Association and to the Association of American Medical Colleges. Both bodies have officially recognized the value of the program in its entirety.

Information concerning any part of the program may be obtained from the Surgeon General's Office. Address requests to the attention of the Chief of Personnel, SGO, Department of the Army, Washington, D. C.





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LESIONS OF BONES AND JOINTS ARISING FROM INTERRUPTION  
OF THE CIRCULATION

DALLAS B. PHEMISTER, M.D.\*

*(Chicago, Ill.)*

Lesions arising from interruption of the circulation in the soft parts and certain organs are widely known and well understood. Familiar examples result from occlusion or in some cases injury of coronary, cerebral, retinal, pulmonary, splenic, renal, superior mesenteric and major extremity arteries. No such generalization can be made for similar lesions of the bones and joints, most of which are less well known and poorly understood.

Bone undergoes aseptic necrosis as the immediate result of injury or occlusion of the blood vessels in the absence of infection. As in cases of infarction of the soft parts, the devascularized tissue dies in the course of a very few days. The idea that the bone may not die until months or years after the injury or occlusion of its blood vessels is wholly fallacious and is the result of assumption that death occurs at the time when differences in density between necrotic and living portions make it possible to recognize the dead bone in roentgenograms, or when a dead articular portion breaks down and becomes displaced from weight-bearing. Both of these phenomena are noted relatively late in the course of aseptic necrosis.

The most frequent cause of aseptic necrosis from injury is fracture, but it may also be produced by dislocation, as of the hip, wrist, or ankle joint; by operation, as arthroplasty of the hip; or extensive stripping of fragments in the operative treatment of fractures (1). A rare cause appears to be sprain or direct trauma to the nutrient vessels as in case of the carpal lunatum.

Occlusion of the blood vessels of bone resulting in aseptic necrosis (2, 3) may be produced by embolism, thrombosis, or localized obliterative vascular disease frequently of an obscure nature, but sometimes on an arteriosclerotic basis.

Fracture of the shaft of the long bones causes a certain amount of necrosis of the cortex of the ends of the fragments and of splinters, but bony union usually occurs in such cases in normal time since the callus is laid down by surviving periosteum and endosteum and the dead bone is subsequently replaced by new bone by a gradual process of creeping substitution. When the fracture involves the end of the bone and the shorter fragment is either entirely or mainly within the joint, its entire circulation may be cut off leading to necrosis of the bone, bone marrow and the articular cartilage. In such cases the callus can be laid down only by the end of the shaft fragment instead of by both fragments, and the incidence of non-union is thereby appreciably increased. Aseptic necrosis from fractures bordering on joints is seen most frequently in the head and neck of the femur,

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Presented as part of a series of lectures on Recent Advances in Surgery, at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on December 3, 1947.

the carpal navicular bone, the astragalus, the capitellum of the humerus, and the head of the radius. Smaller necrotic lesions bordering on the articular surface of various joints may be separated by the trauma of usage and give rise to the picture of osteochondritis dissecans.

Of these lesions, intra-articular fracture of the neck of the femur is by far of the greatest importance. The principal blood supply to the head of the femur comes by way of neck capsule branches of the anterior and posterior circumflex arteries, and when the neck is fractured near the head, all or most of these vessels may be severed regardless of the extent of the displacement of fragments. As a result, there is immediate cutting off of the blood supply to the major portion or all of the head and the proximal neck fragment of the femur. In some cases, the arteries coming by way of round ligament are of sufficient size to maintain the circulation of the head, but more frequently they provide it with little blood supply, so that if the neck is fractured and the capsule completely severed the head becomes necrotic.

If the head becomes necrotic and non-union of the fractured neck follows (5, 6), blood vessels and connective tissue, coming by way of the round ligament, untorn portions of the capsule and adhesions, slowly invade the cancellous spaces of the head, usually at first in the inferior portion and in the vicinity of the fovea. The front line of invading tissue absorbs and replaces the dead marrow, while the second line behaves like callus and differentiates into new bone and marrow. The new bone is laid down on the old dead bone which it slowly absorbs and replaces by the process of creeping substitution. The remaining uninvaded, old dead bone of the lateral and upper portions of the head, having no blood supply, cannot atrophy, and retains its original density as revealed by roentgenograms. The living bone of the distal fragment and any portion of the head which did not have its blood supply severed gradually undergo atrophy as a result of the marked disuse produced by the ununited fracture. Consequently in two to three months it casts a fainter shadow than either the dead bone of the head or any newly formed bone in the head since the latter is very spongy as a result of being deposited in an ununited non-functioning head. This combination of atrophic bone in the distal fragment and of atrophic surviving bone or spongy replacing new bone in the lower portion of the dead head makes it possible to recognize the remaining necrotic portion of the head by the greater density of its shadow cast in roentgenograms. It is incorrect to say that the dead bone has increased in density since the difference is due to a decrease in density of the living bone.

If the ununited fracture is left untreated, the dead bone in the course of time may be slowly replaced by living bone so that after several years only a small amount of it remains, usually in the upper portion of the head. Occasionally a calcified zone is formed about the periphery of such a remnant. But the dead portion never collapses since, because of the non-union, it is non weight bearing. Rarely all of the dead bone is finally replaced by spongy new bone. The articular cartilage, being deprived of its nutrition by tissue fluid derived from the blood supply of the underlying bone, gradually undergoes extensive necrosis, and in the course of time is invaded by blood vessels and fibrous tissue, and replaced by a layer of fibrocartilage.

The management of the necrotic head with non-union depends upon the duration of the fracture at the time when treatment is begun. If seen within the first one or two years while the head usually consists mainly of necrotic bone, (7, Case 9) the fracture may be openly reduced through a Smith-Petersen incision and the fragments fixed by two snugly fitting rectangular tibial bone grafts inserted into 1 cm. holes drilled from the side of the shaft through the neck and deep into or through the upper portion of the head. Additional fixation should be provided by threaded wires or screws similarly inserted from the side obliquely upward into other portions of the head. The drilling of the upper portion of the head as in Figure 4 gets rid of a considerable amount of dead bone and opens the remaining necrotic portion for rapid invasion of the empty space alongside the rectangular grafts by callus and replacement by new bone. The grafts serve as struts to prevent collapse of the upper portion of the head and increase the frequency of union of the fracture of the neck. Following this procedure the dead head may gradually be transformed into living bone and the dead articular cartilage replaced by fibrocartilage with the preservation of the normal contour of the head and the reestablishment of a well functioning hip. Good results might be obtained by fixation with a Smith-Petersen nail inserted through the lower part of the neck and head followed by a bone graft through the upper part. A tubular drill may be used for tunneling the head portion and the core saved as a biopsy specimen for microscopic examination. Crutches should be used for 9 to 12 months or until x-rays indicate that the dead bone has been replaced by new bone.

If the non-union is of 3 or more years standing and the dead bone and dead articular cartilage have been extensively absorbed and replaced respectively by frail new bone and fibrocartilage, it is probably always best to excise the head which is often adherent and frozen in the acetabulum, and perform either one of the various types of arthroplasty or an arthrodesis of the hip.

In case of a fresh fracture of the neck with death of the proximal fragment, bony union usually follows if the fragments are either impacted or are well reduced and well fixed as by a Smith-Petersen nail or threaded pins. The callus and blood vessels grow from the distal fragment into the fracture line and then invade the dead fragment of the neck. After union of the fracture, which is usually solid within 3 months, the blood vessels and callus advance proximally, invade the head, and begin to replace the dead bone by new bone, sometimes fairly rapidly but more frequently slowly. If the patient is kept off the feet for a prolonged period up to as much as 2 or 3 years, all of the dead bone may occasionally be replaced by new bone without collapse of the weight-bearing portion of the head from pressure against the acetabulum, and a well functioning hip may be re-established (8). However, if weight-bearing is permitted, that portion of the head underlying the acetabulum will be broken off when, many months after healing of the fracture, the invading new bone reaches its lateral margin and inferior portions (fig. 1). The fracture takes place in a downward line through the zone of replacing new bone since it is temporarily soft and too weak to stand the weight from the acetabulum. The collapse of the remaining



strong dead portion leads to deformity and a degenerative arthritis and a poorly functioning hip results. The broken off dead portion may eventually become re-attached and replaced by new bone, or fragmented and slowly absorbed, or occasionally it may persist with an ununited fracture line separating it from the underlying replaced portion similar to a loose body from the femoral condyle



FIG. 1. Fracture of neck of femur 2 $\frac{3}{4}$  years previously, treated at onset by nailing. Despite death of the head the fracture united and immediate function was restored to normal. For past 5 months, increasing pain and stiffness in the hip. The lateral and lower portions of head have been replaced by new bone but the weight bearing upper portion has broken off beyond Smith-Petersen nail. Nail was then removed and two bone grafts inserted through necrotic field.

in osteochondritis dissecans at the knee. In a certain percentage of cases of fracture of the neck with aseptic necrosis in which pin or nail fixation is employed, the fracture fails to unite, the pin loosens and the neck is slowly eroded and shortened. In other cases, the fracture unites but months later a re-fracture occurs a short distance proximal to the old fracture line as weight is thrown upon the weak invading zone of new bone.

The roentgenographic recognition of a dead head produced by fracture of the neck is much more difficult if the fracture unites than if it remains ununited (7). This is because when the fracture unites and the limb is used there is little atrophy of disuse of the distal living fragment and its density is only slightly less than that of the dead avascular head which cannot atrophy. On the other hand, in case of non-union there is little use made of the extremity and the distal living bone undergoes marked atrophy of disuse in consequence of which it casts a much fainter shadow than that of the dead head.

Aseptic necrosis of bone produced by lesions other than tearing the blood vessels in injuries is relatively common in certain epiphyses and short bones during childhood and adult life. Familiar examples are Legg Perthes' disease of the hip, Osgood-Schlatter's disease of the tibial tubercle, Kohler's disease of the tarsal navicular and the metatarsal bones, and Calve's disease of the vertebral bodies. These lesions form a special group and will not be further discussed.

Non-traumatic aseptic necrosis in adults is less frequent than that in children and presents a somewhat different clinical picture. The etiology in the majority of cases is obscure. The best known cause is caisson disease (3) in which the excess nitrogen taken up by the blood and tissue fluids during the period spent by the worker in compressed air is liberated as a gas when decompression is too rapidly brought about. The exact method in which the gas acts upon the bones is imperfectly understood. It may be through arterial embolism or through direct pressure of the intramedullary gas liberated from the bone marrow which is rich in fat that absorbs the nitrogen under pressure in large quantities. The lesions are located in the long bones of the extremities and may affect either epiphysis or diaphysis, and not infrequently both epiphysis and diaphysis of one or several bones. The most frequent sites are the head and neck of the femur, the head of the humerus, the lower end of the femur, the upper and lower ends of the tibia, and the upper end of the shaft of the humerus. The bones of the trunk and the short bones of the extremities are practically never involved.

Large infarcts bordering on the articular cartilage are common in the head of the femur (fig. 4) and humerus and are frequently bi-lateral. Large to small infarcts are found less frequently in the shafts of humerus, femur and tibia, and rarely in the fibula. The infarcts of the shaft are gradually invaded about the periphery by blood vessels and fibrous tissue with properties similar to callus. They occupy the cancellous spaces and absorb the dead marrow and cancellous trabeculae, replacing them by living trabeculae and living marrow. This creeping replacement of the dead bone by new bone may continue over periods from months to 2 or more years, and it may involve inner portions of cortex which has lost its circulation. Small infarcts may be completely replaced. But with large infarcts, when the replacement process has advanced to the point at which the involved bone has regained its normal strength, the reparative stimulus may be exhausted. Then large to small areas of dead bone may be left permanently (figs. 2 and 3), and calcification of the fibrous zone of invasion about the periphery and of small islands of the dead interior may come about much as in the case of old infarcts of the spleen or kidney. Infarcts of the diaphyses

produce little or no symptoms and cannot be diagnosed clinically until years after their formation when the calcified areas cast heavy shadows in roentgenograms that are characteristic of the lesion.



FIG. 2. Roentgenogram of femur showing calcified infarct 35 years after severe caisson disease.

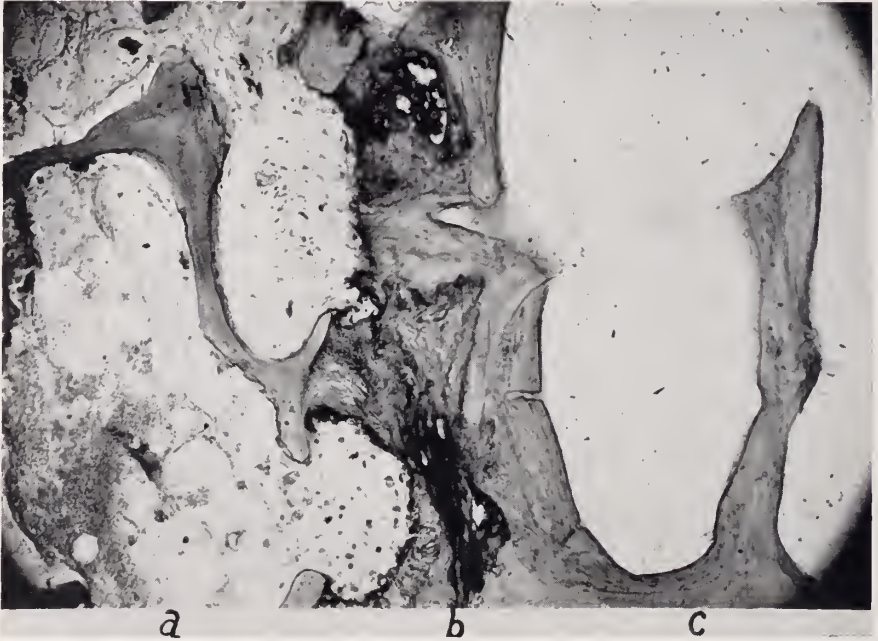


FIG. 3. Microscopic section of wall of infarct shown in Figure 2: a. Periphery of the infarct showing dead necrotic bone and partially calcified necrotic marrow; b. Calcified old zone of replacement; c. Living bone outside the infarct.

The aseptic necrosis of the head of the femur usually involves the entire structure including bone and its overlying cartilage, although in some instances small portions of the lower part of the head appear to remain alive. Following the occurrence of embolism, there is gradual invasion of the dead bone of the head by blood vessels and callus-like tissue coming from the neck and sometimes from the round ligament with replacement of the dead bone and dead marrow by

living bone and living marrow similar to that described for infarcts of the shaft. Weight bearing throughout this period results in breaking down of the head and deforming arthritis. If there has been replacement of the inferior and inferomesial portions by invasion from untorn inferior neck capsule and round ligament invasion, the necrotic portion may break off extending bowl-shaped downward from the top of the head (fig. 4). These changes are illustrated in reference 3 of the bibliography.

Single or, more frequently, multiple infarction of epiphyses and diaphyses similar to that produced by caisson disease may be produced by vascular occlusion from other causes, most of which are very obscure (4). In some cases the lesions develop in elderly individuals affected by cardiovascular disease, and obliterative arteriosclerosis may be the direct cause of the infarction. There is little evidence that multiple arterial embolism has been the exciting cause in the few cases that have come to autopsy, since embolic infarction of the soft tissues which might



FIG. 4. Necrosis of heads of femurs, 3½ years after attack of caisson disease. Dead head replaced by new bone in the lateral, inferior and foveal regions. Upper and central necrotic portion broken off by weight bearing from acetabulum.

be expected as an accompaniment has not been found. Rheumatic fever and rheumatic heart disease may have been a factor in one of the cases studied. Single or multiple infarction has been accompanied by degenerative arthritis in joints remote from the lesions with sufficient frequency to suggest an etiological relationship between the two conditions. Illustrations of this group of cases are to be found in references (2) and (4). Further studies will be necessary before the causes of multiple non-traumatic aseptic bone infarction are understood.

The clinical course and management of necrosis of the head of the femur are much the same whether in fractures of the neck of the femur followed by bony union, dislocations of the hip, or non-traumatic lesions such as caisson disease and obscure obstructive arterial disease. The callus-like fibrous tissue which grows from the neck or surviving portion of head into the dead head slowly absorbs and replaces the dead bone by new bone. During the initial stages of invasion and replacement, the changes proceed asymptotically and there is little interference with function of the hip. The head of the bone retains its contour and density and the condition frequently can usually not be recognized



in roentgenograms. After several months to a year or two the invading new bone in all of these conditions reaches the weight-bearing part of the head from from the lateral and inferior portions, and as the stress from the acetabulum is thrown upon the zone of replacing new bone it fractures because it is initially weaker than the old dead bone which it has replaced (5, Case 5). The broken off portion of dead bone lying beneath the acetabulum then begins to collapse from further weight bearing. If roentgenograms are taken as soon as the hip becomes painful, the occurrence of the fracture may be recognized early while there is very little displacement, and the opportune time for treatment is at hand. If further weight bearing is permitted, the broken off dead bone will be downwardly displaced, the head gradually deformed, and degenerative arthritis set up. Patients with beginning collapse of the head have been placed on crutches and forbidden weight bearing over long periods up to two or three years, but despite this drastic therapy the head usually flattens to some extent and deforming arthritis is established, leaving a somewhat painful and poorly functioning hip. The ideal treatment in this early stage of recognition should aim at the prevention of further collapse of the head and rapid replacement of the dead bone by new bone and of the dead articular cartilage by fibrocartilage.

Recently in a small number of cases an operation has been employed similar to that described for ununited fracture of the neck with death of the head which has yielded results superior to those obtained by most of the methods in common practice. The lateral surface of the shaft is exposed through a 6 inch incision extending downward from the greater trochanter. With x-ray control, a 1 cm. drill hole is made extending obliquely upward and inward through the superior portion of the neck and head, perforating the overlying articular cartilage. A second drill hole is started about  $2\frac{1}{2}$  cms. below the first and directed slightly more obliquely upward so that it perforates the articular cortex and cartilage approximately 1 cm. below the first drill hole. If a Smith-Petersen nail has been used and the fracture has united but the top of the head has later collapsed, the nail is removed and one drill hole is made along its channel. Two bone grafts, each slightly less than 1 cm. broad and slightly longer than the length of its tunnel, are taken from the antero-mesial surface of the tibia and inserted sagittally into the tunnels ending just short of the articular surface. The wound is closed and the patient is kept on crutches for 9 months to a year depending on the clinical course and the appearance shown in roentgenograms. The drill removes a considerable portion of the dead bone. The grafts act as strong struts to prevent collapse of the upper portion of the head during the period of invasion and replacement by new bone. There is room between the walls of the round holes and the rectangular pegs for the ingrowth of blood vessels and callus from the neck side into the remaining dead bone of the head. This brings about a relatively rapid invasion and transformation of what is left of the dead head, and fibrous tissue grows out of the proximal end of the hole onto the articular surface, invading, absorbing and replacing the dead articular cartilage by fibrocartilage. Thus a live head of approximately normal strength and contour is relatively rapidly re-created, and degenerative changes in the hip joint are reduced to a



minimum. One patient treated in this way has x-ray signs of a reconstructed head and an excellent clinical result characterized by freedom from pain with almost a normal range of motion and good weight bearing at the end of one year.

If the patient is not seen until late when the head of the femur is broken down and the joint is badly crippled, another type of operation may be indicated, such as a vitallium cup or other arthroplasty or arthrodesis of the hip joint.

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# DELAY IN THE FORMATION OF HIPPURIC ACID FROM BENZOIC ACID IN PATIENTS WITH LIVER DAMAGE<sup>1</sup>

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The oral hippuric acid test has become one of the standard methods of gauging liver function (1). In this test 5.8 Gm. of sodium benzoate (equivalent to 5 Gm. of benzoic acid) are dissolved in water and ingested by the patient. The average normal adult will excrete in the urine about 3 Gm. of benzoic acid in the form of hippuric acid in a 4-hour period, with a normal variation of from 85 to 110 per cent of this value. The latter depends on the size of the patient (2, 3).

In one of Quick's early publications, he noted that one of his patients with post-arsphenamine jaundice (mild hepatitis) "had an increased output of hippuric acid, which suggested abnormal stimulation rather than a depression of function" (2).

Rosenberg and Soskin (4), in a study of 100 patients with clinical findings of mild and moderate grades of hepatic disease, have shown that the incidence of abnormal excretion of hippuric acid (increased and decreased excretion combined) was as great as the incidence of abnormal bromsulphalein tests in the same group of patients.

Hepler and Gurley (5) expressed doubts concerning the evidence for increased output of hippuric acid. From their results, obtained by an improved technique, they conclude that 90 per cent of three grams should be the lower limit of normal and there should be no upper limit for normal. Other investigators have been puzzled by the relatively normal hippuric acid excretion during the acute stage of an infectious hepatitis, followed by low results during convalescence (6).

In the experiments to be described the authors have examined the conjugation of benzoic acid with both glycine and glucuronic acid using fractional urine collections after administration of 5 Gm. of benzoic acid. It will be shown that a delay in the formation of hippuric acid is often present in the milder forms of hepatic damage. The results obtained suggest an explanation for the apparent discrepancies in previous reports on the value of the hippuric acid test.

## METHOD

Fasting patients ingested 5 Gm. of benzoic acid (not sodium benzoate) wrapped in moistened powder wafers. The same dose can be given in 8 gelatin capsules (No. 0) without alteration of results. The wafers or capsules were swallowed with a glass of water, the total quantity being ingested within 10 minutes.

Following the ingestion of the benzoic acid three 2-hour specimens of urine were carefully collected. If the urine volume of any specimen was very small, less than 50 ml., the entire test was repeated. Hippuric acid was determined by a gravimetric method and the presence of benzoyl glucuronic acid demonstrated

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<sup>2</sup> Assisted by a fellowship from the Emanuel Libman Fellowship Fund.

by a qualitative test employing naphthoresorcinol. Details of both methods have been described (7).

Glucose infusions were discontinued, and food was withheld until completion of the test.

#### OBSERVATIONS

Table I gives the minimum, average, and maximum values for hippuric acid excretion in 15 entirely normal subjects after ingestion of 5 Gm. of benzoic acid. The normal pattern of excretion is characterized by: (1) The first 2-hour specimen is over 1 Gm. (1.00–2.60 Gm.); (2) the largest value is in the second 2-hour specimen (1.90–4.36 Gm.); (3) the third 2-hour specimen contains definitely less hippuric acid than the second 2-hour specimen (0.02–2.20 Gm.); (4) the total excretion of hippuric acid in 6 hours is 5 Gm. or more (equivalent to 3.4 Gm. of benzoic acid or more). It was soon noted that a normal total 6-hour value by itself did not necessarily signify that the rate of conjugation was normal.

TABLE I

*Hippuric acid excretion in fifteen normal subjects after ingestion of 5 Gm. of benzoic acid\**

SPECIMEN	2 HR.	4 HR.	6 HR.	TOTAL 6 HR.
Minimum.....	1.00	1.90	0.02	5.06
Maximum.....	2.60	4.36	2.20	7.15
Average.....	1.84	3.01	1.19	6.04
Glucuronides†.....	—	±	—	

\* All values are given in grams of hippuric acid.

† Qualitative test employing naphthoresorcinol.

In Table II examples of hippuric acid and glucuronide excretion after ingestion of 5 Gm. of benzoic acid by patients with various degrees of liver damage are given. An abnormal glucuronide pattern (8), that is, excessive excretion of glucuronic acid, was obtained in 52 out of 59 patients diagnosed as infectious hepatitis, cirrhosis, hyperthyroidism, or malignant metastasis to the liver. Forty-one of this group excreted less than 5 Gm. of hippuric acid. Many had deviations in distribution of hippuric acid excretion in the three 2-hour specimens as compared to normal. From an examination of the 25 patients with hepatitis, both acute and subsiding, it was noted that in 17 cases the first 2-hour specimen contained less than the normal minimum, that is, 1.00 Gm. hippuric acid. Nevertheless 6 of these 17 cases excreted more than 5.00 Gm. of hippuric acid in 6 hours. In 4 of the remaining 8 cases of hepatitis the second 2-hour specimen contained less than the normal minimum, that is, 1.90 Gm. of hippuric acid. Two of these 4 cases excreted more than 5.00 Gm. of hippuric acid. In 4 patients all three 2-hour specimens contained quantities of hippuric acid which were within normal limits. In all 4 patients the glucuronide reactions were definitely abnormal. It follows that the total excretion of hippuric acid in 6-hour specimens was normal in 12 of 25 cases of hepatitis. In 6 of these 12 cases examination of the 2-hour specimens showed that the liver function was impaired.

TABLE II

*Hippuric acid and glucuronides\* in patients with liver dysfunction after ingestion of 5 Gm. benzoic acid*

	GRAMS OF HIPPURIC ACID IN			
	2 hours	4 hours	6 hours	Total 6 hours
Infectious Hepatitis				
1.	0.65	1.00	2.03	3.68
	—	+++	+++	
2.	0.56	2.17	0.72	3.45
	+	+	—	
3.	0.59	3.70	1.24	5.53
	—	+++	—	
4.	1.08	1.64	2.95	5.67
	—	++	+++	
5.	0.60	1.64	2.76	5.00
	—	+++	+++	
6.	1.29	1.35	1.43	4.07
	—	+++	++	
7.	1.92	1.98	1.17	5.07
	++	+++	++	
8.	0.97	2.22	2.03	5.22
	—	++	+++	
9.	0.55	0.93	1.35	2.83
	—	++	+	
10.	0.67	2.99	1.78	5.44
	—	+++	+++	
11.	1.60	2.14	0.80	4.55
	+++	+++	++	
12.	0.61	1.56	1.49	3.06
	—	+++	+	
13.	0.74	0.91	1.29	2.94
	—	—	+	
14.	0.61	0.58	0.70	1.89
	—	—	+	
15.	0.43	0.66	0.82	1.91
	—	+	++	
16.	0.87	1.57	1.32	3.76
	—	+++	+++	
17.	0.37	1.41	0.87	2.65
	—	++	+	
18.	1.00	1.79	1.30	4.09
	—	—	++	
19.	0.54	1.24	3.59	5.37
	—	—	+++	
20.†	0.62	1.35	0.70	2.67
	—	—	—	
21.†	1.07	2.25	1.63	4.59
	+	+++	++	
22.†	0.50	1.94	1.39	3.83
	—	—	—	

TABLE II—Continued

	GRAMS OF HIPPURIC ACID IN			
	2 hours	4 hours	6 hours	Total 6 hours
Infectious Hepatitis				
23. †	1.96 ++	2.57 ++	1.67 —	6.40
24. †	1.35 —	1.64 —	2.35 —	5.34
25. †	0.92 —	4.82 —	1.35 —	7.07
Portal Cirrhosis				
1.	0.29 —	0.30 —	3.39 +++	3.98
2.	0.85 ++	0.97 ++	1.33 —	3.15
3.	1.22 +	1.42 ++	1.29 +++	3.83
4.	0.28 —	2.43 ++	1.66 +	4.37
5.	0.27 —	0.34 ++	1.02 +	1.63
6.	0.83 +++	1.04 +++	0.69 —	2.56
7.	1.00 —	1.41 +	1.87 ++	4.28
8.	1.05 —	1.20 +++	1.02 ++	3.27
9.	1.02 —	2.93 +++	1.83 ++	5.78
10.	0.53 —	0.96 —	1.60 +	3.09
11.	1.10 —	1.59 —	2.20 +	4.89
12.	0.87 ++	1.22 —	1.32 —	3.41
13.	0.21 —	1.45 —	1.44 +	3.10
14.	1.47 +	1.51 +	1.14 +	4.12
15.	0.19 —	1.02 —	2.08 —	3.29
16.	0.49 —	1.01 —	0.96 —	2.46
Metastasis, Liver				
1.	0.98 —	2.14 ++	2.26 —	5.38
2.	0.94 +	1.14 +	1.73 ++	3.81
3.	0.57 —	3.51 +++	1.32 +	5.40



TABLE II—*Concluded*

	GRAMS OF HIPPURIC ACID IN			
	2 hours	4 hours	6 hours	Total 6 hours
Metastasis, Liver				
4.	0.32	1.13	1.84	3.29
	—	—	++	
5.	1.26	1.00	0.29	2.55
	+++	++	+	
6.	0.17	2.10	1.34	3.61
	—	—	+	
7.	0.21	0.51	0.68	1.40
	++	—	—	
8.	0.66	1.59	0.89	3.14
	—	—	—	
Hyperthyroidism				
1.	2.45	1.69	0.38	4.52
	—	+	—	
2.	2.69	0.47	0.91	4.07
	++	—	—	
3.	2.32	1.71	2.21	6.24
	+++	+++	++	
4.	2.31	1.16	0.04	3.51
	++	—	—	
5.	1.12	1.27	2.00	4.39
	—	—	+++	
6.	1.07	2.39	2.31	5.77
	—	++	++	
7.	1.16	2.38	1.21	4.75
	+	+++	—	
8.	0.70	2.83	1.49	5.02
	—	++	—	
9.	1.90	3.48	0.64	6.02
	+++	+++	—	
10.	1.49	3.33	0.99	5.81
	—	+++	+	

\* The plus and the minus signs refer to the results of the qualitative test for glucuronides.

† Subsiding.

In 10 out of the 16 cases of portal cirrhosis the first 2-hour specimen contained less than the normal minimum, that is, 1.00 Gm. hippuric acid. In 5 of the remaining 6 cases of cirrhosis the second 2-hour specimen contained less than the normal minimum, that is, 1.90 Gm. hippuric acid. In only 1 patient (No. 9) were the quantities of hippuric acid in all three 2-hour specimens within normal limits. This is the only patient who excreted more than 5.00 Gm. of hippuric acid in 6 hours. The glucuronide excretion of this patient was definitely abnormal.

There were 8 cases of jaundice due to liver metastasis. In 7 cases the first 2-hour specimen contained less than the normal minimum, that is, 1.00 Gm.

hippuric acid. Two of these cases excreted more than 5.00 Gm. of hippuric acid in 6 hours.

The existence of 3 types of abnormal distribution of hippuric acid is illustrated in Fig. 1: (I) First specimen contains the largest quantity; this type is found only in hyperthyroid patients. (II) The first 2-hour specimen contains less than 1 Gm., and an abnormally large amount of hippuric acid is found in the second 2-hour specimen. (III) First specimen is low, second is higher, third specimen largest; after a delay the liver, if not severely damaged, produces a relatively large quantity of hippuric acid.

It is well known that the hippuric acid test is a measure of both production of glycine and conjugation of the latter with benzoic acid (9). Thus Probst and Londe (10) observed an increase in the rate of hippuric acid synthesis in normal

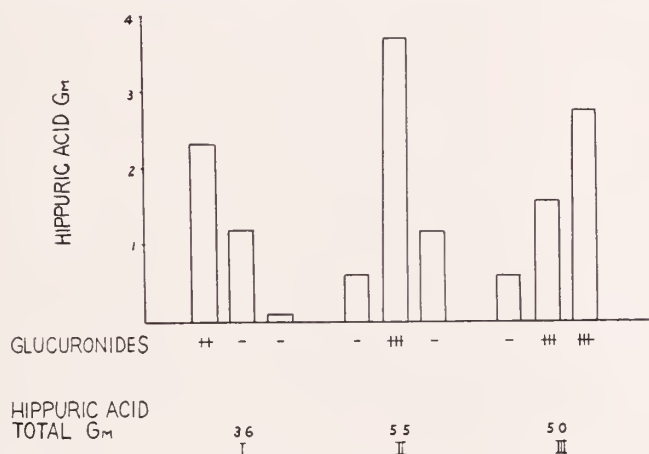


FIG. 1. Three types of abnormal distribution of hippuric acid excretion after ingestion of 5 Gm. of benzoic acid in patients with liver damage.

I Patient with hyperthyroidism

II Patient with portal cirrhosis

III Patient with infectious hepatitis

adults and in 24 of 30 patients with diminished hippuric acid excretion when glycine was given along with the benzoate. In the remaining 6 patients there was no increase in rate. The latter finding suggested that in severe liver insufficiency both the formation and the conjugation of the glycine were impaired. Barker, Capps, and Allen (6) confirmed these observations recently, having obtained a normal hippuric acid excretion in 153 out of 156 patients with hepatitis who were given glycine with the test. The importance of ingested glycine for the synthesis of hippuric acid in the human being does not tally completely with the results of animal experiments. Even if large amounts of glycine are given, the liver of the rat will produce hippuric acid containing glycine which is not of dietary origin. This was shown by Rittenberg and Schoenheimer (11) in experiments with rats fed an excess of glycine labelled with heavy nitrogen. They found that only one-third of the glycine which was conjugated with the benzoic acid was of dietary origin. The experiments of Barker and associates indicate that the human liver, especially if damaged, may well react differently.

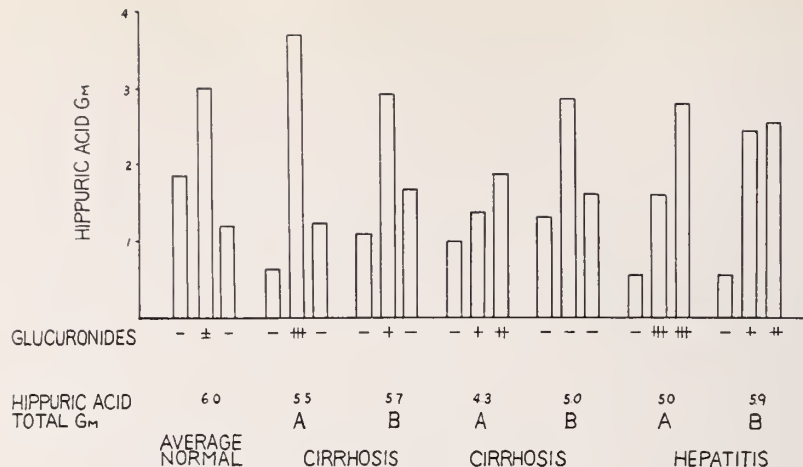


FIG. 2. Excretion of hippuric acid and glucuronides by patients with liver disease after ingestion of benzoic acid 5 Gm. (A), and benzoic acid 5 Gm. preceded by glycine 5 Gm. (B).

TABLE III

*Hippuric acid and glucuronides\* after ingestion of sodium benzoate 5.8 Gm.*

	GRAMS OF HIPPURIC ACID IN			
	2 hours	4 hours	6 hours	Total 6 hours
Normal†				
Minimum	2.81	2.24	0.00	5.81
Maximum	4.70	3.45	0.71	7.54
Average	3.76	2.74	0.28	6.78
Glucuronides	+++	+	—	
Patients				
1. Cirrhosis	1.21	1.11	0.64	2.96
	—	++	++	
2. Cirrhosis	1.26	1.85	1.62	4.73
	—	+++	+++	
3. Cirrhosis	1.81	2.12	1.82	5.75
	+++	+++	++	
4. Subacute yellow atrophy	0.14	0.21	0.18	0.53
	++	+++	+++	
5. Hepatitis	0.78	0.72	1.43	2.93
	+	+++	+++	
6. Lymphoblastoma	1.56	2.32	0.48	4.36
	++	+	—	
7. Cirrhosis	1.04	1.58	1.64	4.26
	—	++	++	
8. Cirrhosis	0.66	1.15	1.08	2.89
	—	+++	+++	
9. Cirrhosis	0.48	2.93	1.16	4.57
	+++	+++	++	
10. Hepatitis	0.86	0.84	3.57	5.27
	+++	+++	+++	
11. Hepatitis	0.43	2.96	2.23	5.62
	+	+++	+++	

\* The plus and minus signs refer to the results of the qualitative test for glucuronides.

† Nine normal subjects (7).

As shown in Fig. 2 administration of 5 Gm. of glycine to patients with hepatic dysfunction one-half hour before benzoic acid ingestion not only yielded hippuric acid curves approaching the normal, but at the same time decreased the excretion of glucuronides.

For comparison with results obtained after ingestion of *benzoic acid*, the hippuric acid distribution after oral administration of *sodium benzoate* was examined using a similar fractional 6-hour collection period. Table III indicates that 6 of 11 patients with liver disease show the type of conjugation where a relatively large amount of hippuric acid is synthesized after a lag period. We note that in patients 5, 7, and 10 the value for the third 2-hour specimen was greater than that for either of the 2 preceding specimens. In all patients the first 2-hour specimen contained less than 2.0 Gm. of hippuric acid, that is, less than the minimal value found in our series of normal individuals (2.8 Gm.). This also held true for the 3 patients who showed a normal total hippuric acid excretion in the course of 6 hours (more than 5 Gm.).

#### COMMENT

Quick has shown that in normal subjects, irrespective of the dose of sodium benzoate administered, the maximum amount of hippuric acid formed per hour is practically constant (11, 12). In his original test 5.8 Gms. of sodium benzoate are given—a quantity which is in excess of the liver's capacity to conjugate within a fixed period of time. For normal subjects a total 4-hour value after oral ingestion, and a one-hour value after intravenous injection, is optimal for the measurement of the functional capacity of the liver in this synthesis. However, it does not follow that the rate of hippuric acid production is relatively constant in all patients with liver disorders. Close examination of Quick's published data yields a number of instances of gradually increasing rates of synthesis rather than constant rates (hourly determinations being done for a four-hour period). In one publication (2) 20 out of 35 cases of hepatic disease exhibited this phenomenon as compared to 5 out of 41 control patients who were without apparent liver involvement. In a later publication (3) data on 3 patients with liver disease were presented; 2 had increasing rates of synthesis.

The authors have presented evidence to divide impairment of hippuric acid formation into two stages: (1) delayed production of normal or near-normal amounts of hippuric acid by increasing rates of synthesis; (2) diminished production of hippuric acid. An additional and compensatory process often present is the greater use of the benzoyl glucuronic acid conjugation by the damaged liver. Our experience is that in a very few instances of mild parenchymal liver damage there was no increased glucuronide excretion. In these instances the impairment of the liver function was indicated by a delayed formation of hippuric acid.

When glycine was administered, the abnormal rates of conjugation were brought nearly to normal. This again draws attention to the glycine availability. It also makes faulty intestinal absorption of benzoate unlikely.

By determining the hippuric acid excretion obtained at 2-hour intervals after ingestion of 5 Gm. of benzoic acid, it is possible to demonstrate abnormalities of the hippuric acid synthesis even in patients who excrete a normal total amount of

hippuric acid. The rate of hippuric acid synthesis in hepatocellular disease is not necessarily constant; often a conspicuous acceleration will occur after a lag period. Thus the reliability of single determinations of the total hippuric acid excretion in 4 hours as an index of the *degree* of liver damage can be questioned. If one wishes to use the hippuric acid synthesis as a liver function test, a fractional method, which was the way the test was originally introduced by Quick (1), is an essential requisite. Furthermore, a fractional method of 6 hours covers the period for hippuric acid synthesis more adequately than the usual 4-hour method. This makes the test a rather cumbersome one. The difficulties of collecting complete 2-hour specimens should also not be underestimated. The increased glucuronide excretion after ingestion of 5 Gm. benzoic acid is a simpler and more reliable test.

#### SUMMARY

1. Fractional determinations of the excretion of hippuric acid in the urine were made after ingestion of 5 Gm. of *benzoic acid*. The normal range of values is given.

2. In many cases of hepatic disturbances a delayed hippuric acid synthesis was found even when the total hippuric acid excretion was not decreased.

3. Delayed formation of hippuric acid was also seen after the ingestion of *sodium benzoate*, and is offered as a partial explanation for the reported discrepancies obtained with the test.

4. The reliability of a single determination of the total hippuric acid excretion during a 4-hour period as an index of the degree of hepatic damage, is questioned.

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# THE EFFECTS OF ANTERIOR PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) IN MYASTHENIA GRAVIS WITH TUMOR OF THE THYMUS.<sup>1</sup>

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This communication deals with the results of the administration of anterior hypophyseal adrenocorticotrophic hormone (ACTH) to a patient with myasthenia gravis with a thymic tumor. The patient was admitted to the Metabolism Ward of The Mount Sinai Hospital for balance studies which extended over a 52 day period. The investigation particularly concerned itself with the effect of the adrenocorticotrophic hormone on: 1) The size of the thymic mass; 2) the myasthenic symptoms and daily prostigmine requirements; 3) the urinary excretion of creatine and creatinine following the administration of 2.64 Gm. of creatine; 4) the urinary excretion of the neutral 17-ketosteroids and the urinary excretion of those steroid compounds with a 3-keto-pregnene grouping extractable from neutral urine<sup>4</sup>; 5) the blood and urine electrolytes (sodium and chloride) under control conditions, on a relatively salt free intake (200 mg. sodium daily), and following the administration of a measured amount of salt (8 Gm. daily); 6) the peripheral white blood cell counts, differential counts, and hematocrit determinations.

## METHODS

The adrenocorticotrophic hormone<sup>5</sup> was administered in the dosage of 10 mg. dissolved in 1 cc. of normal saline every 6 hours day and night for 4 days. The patient, therefore, received a total of 160 mg. extending over a 4 day period. The powdered adrenocorticotrophic hormone was kept in the refrigerator and was prepared for use immediately before the injection. All injections were given intramuscularly and were followed by slight burning and redness at the site of injection. There were only occasional constitutional symptoms, such as mild abdominal cramps and, in one or two instances, a feeling of faintness.

The patient was kept on a constant diet with a measured intake of sodium and chloride. Urine specimens were collected over 3 day periods and appropriately preserved for the various determinations. The urinary ketosteroids were determined by the method of Callow, Callow, and Emmens (1); the 3-keto- $\Delta_4$  pregnene compounds by the method of Laqueur, Jacobs, and Soffer (2); and the blood and urine sodium, chloride, and the urinary creatine and creatinine by standard techniques. The size of the mediastinal mass was

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<sup>4</sup> Such compounds include desoxycorticosterone, 5,16-pregnenediol-3-one-20, and the 11-oxysteroids. Testosterone and progesterone would be included in this group but they are not known to be excreted in the urine as such but only as spectroscopically non-detectable derivatives such as androsterone and pregnandiol.

<sup>5</sup> The adrenocorticotrophic hormone was supplied through the kindness of Dr. John Mote of the Armour Laboratories.

carefully followed by identical x-ray techniques, chest plates being taken during both the cardiac systole and cardiac diastole.

#### CASE REPORT

*History.* The patient was a 29 year old white female. For the past year she had noted drooping of the eyelids, difficulty in speaking, and inability to raise the arms. The symptoms began rather suddenly when, on the patient's wedding anniversary, she noted a drooping of the left eyelid which disappeared after 3 or 4 days. The patient was then apparently symptom-free for the next 3 months, when she again noticed a ptosis of the left eyelid. This time, in addition, she had marked thickness of speech. These symptoms lasted for 2 weeks and then disappeared. Two months prior to admission to the hospital she again developed ptosis of the left lid and thickness of speech. She now complained of marked weakness of the upper extremities and encountered great difficulty in combing her hair, dressing the children, or doing any housework. She consulted a physician, who gave her an injection of prostigmine with striking relief of the symptoms. She was then placed on oral prostigmine, which continued to relieve her of the symptoms. One half hour after taking prostigmine the patient felt "as though I had never been ill." However, the daily prostigmine requirement increased during the next several weeks, and at the time of admission to the hospital she required from 210 to 300 mg. of prostigmine daily. She had been on this therapy for approximately 4 months.

*Examination.* The patient was a well developed young woman who, at the time of the examination, was in no apparent distress and physical examination was essentially negative. There were no muscular fibrillations or atrophy. The thyroid was not enlarged. X-ray studies of the chest revealed the presence of a mass in the anterior mediastinum, extending to the left of the left sternal border between the second and fourth ribs. The hemoglobin was 13.5 Gm., and the white blood cell count and differential study were quite normal. The serum cholesterol was 229 mg. per cent, the total protein 7.0 Gm. per cent, urea nitrogen 7.0 and sugar 84 mg. per cent. The urinary creatine was 62.6 and the creatinine 615.4 mg. in 800 cc. of urine volume. The basal metabolic rate was plus 6 per cent. During her hospital stay the diagnosis of myasthenia gravis was confirmed by careful neurological investigation, although a quinine provocative test failed to produce the characteristic result.

#### THERAPEUTIC RESULTS

*Effect of Adrenocorticotrophic Hormone on Serum and Urinary Sodium and Chloride and on the Hematocrit.* During the salt-free periods prior to the administration of adrenocorticotrophic hormone (ACTH) there occurred a marked diminution in the urinary excretion of sodium and chloride (chart I and table I). With an intake of 8.7 mEq. of sodium and chloride daily (200 mg.) the daily urinary excretion of these ions was 4.6 and 14.8 mEq. respectively. During this period of salt deprivation there occurred very little change in serum sodium and chloride, but an appreciable increase in the hematocrit. Following the administration of a measured amount of salt daily (102.6 to 140.2 mEq. of sodium and chloride, or 6 to 8 Gm.) the urinary excretion of these ions was increased, the hematocrit returned to the control level, but the serum electrolytes remained relatively unaffected. This behavior pattern is identical with that observed in normal individuals under similar experimental circumstances.

The patient was then given 40 mg. of adrenocorticotrophic hormone daily in 4 equally divided doses for 4 days. During this period of therapy she was again kept on the salt-free diet as above. The daily urinary excretion of sodium now fell to 1.6 mEq. and of chloride to 6.7 mEq. With this there occurred an

appreciable decrease in the daily urine volume, a reduction in the serum sodium and chloride, and a proportionate decrease in the blood hematocrit. The urinary excretion of the electrolytes was considerably less than that observed during the salt-free period when the adrenocorticotrophic factor was not administered. The ostensible reduction in serum electrolytes was an expression of the fluid retention and hemodilution which occurred following the administration of the adrenocorticotrophic hormone. These results are similar to those obtained by Forsham and his group (3) in normal individuals, although Mason and his co-workers (4) found the electrolyte metabolism to be essentially undisturbed following the daily administration of 100 mg. of adrenocorticotrophic hormone to a normal woman.

TABLE I

*The Influence of ACTH on the Urinary Excretion of Sodium and Chloride on a Low Daily Salt Intake (200 mg. Na)*

	AVERAGE DAILY URINARY EXCRETION BEFORE TREATMENT WITH ACTH	AVERAGE DAILY URINARY EXCRETION DURING TREATMENT WITH ACTH
Cl (mEq.).....	14.8	6.7
Na (mEq.).....	4.6	1.6

TABLE II

*The Influence of ACTH on the Urinary Excretion of the Neutral 17-Ketosteroids and the 3-keto- $\Delta_4$  pregnene Compounds*

	AVERAGE DAILY URINARY EXCRETION BEFORE TREATMENT WITH ACTH	AVERAGE DAILY URINARY EXCRETION DURING TREATMENT WITH ACTH
Neutral 17-ketosteroids (mg.).....	6.2	20.0
3-keto- $\Delta_4$ pregnene Compounds (gamma).....	8.0	38.0

*Effect of the Administration of Adrenocorticotrophic Hormone on the Urinary Excretion of the Neutral 17-ketosteroids and 3-keto- $\Delta_4$  Pregnene Compounds.* Following the administration of the adrenocorticotrophic hormone there occurred a marked increase in the urinary excretion of both groups of compounds. Prior to injection of the hormone, the daily urinary excretion of the neutral 17-ketosteroids during 4 different metabolism periods was 7.0, 7.0, 5.1, and 5.7 mg. daily. During the period when adrenocorticotrophic hormone was being injected, the 24 hour urinary excretion of neutral 17-ketosteroids rose to 20.0 mg., an almost fourfold increase. There occurred a similarly marked increase in the urinary excretion of the 3-keto- $\Delta_4$  pregnene compounds (chart I and table II).

*Effect of Adrenocorticotrophic Hormone on the Urinary Excretion of Creatine and Creatinine.* The daily urinary excretion of creatine and creatinine during the control balance periods was quite normal, the urinary excretion of creatine averaging 200 mg. daily and that of creatinine averaging approximately 1.0 Gm. The basal urinary excretion of these substances was not affected by the variations

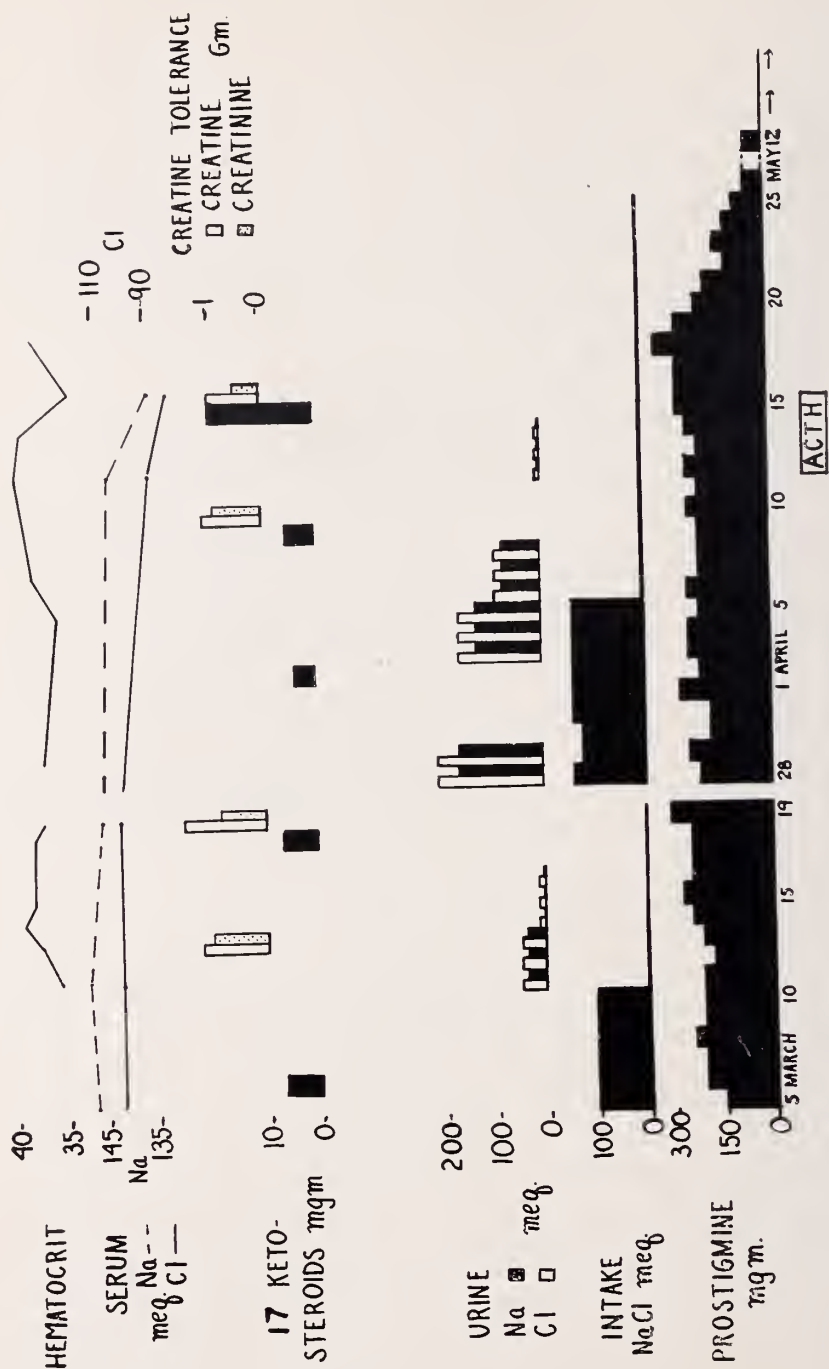


Chart I

in the daily salt intake. Following the administration of 2.64 Gm. of creatine as a creatine tolerance test, there occurred a marked increase in the urinary excretion of creatine, while the degree of creatinine excretion in the urine remained unaffected. There seemed to be a slight decrease in the urinary excretion of creatine with the creatine tolerance test while the patient was on a salt free diet. With the administration of adrenocorticotrophic hormone there occurred only a very slight decrease in the urinary excretion of creatine while on the creatine tolerance test, but there was a marked reduction in the excretion of creatinine (chart I and table III).

*Effect of Adrenocorticotrophic Factor on the Peripheral White Blood Cell Count and Differential Study.* Following the administration of adrenocorticotrophic

TABLE III  
*The Influence of ACTH on the Creatine Tolerance Test*

	AVERAGE DAILY URINARY EXCRETION BEFORE TREATMENT WITH ACTH	AVERAGE DAILY URINARY EXCRETION DURING TREATMENT WITH ACTH
Creatine (Gm.).....	1.37	1.02
Creatinine (Gm.).....	0.99	0.52

TABLE IV  
*The Influence of ACTH on the Total White Blood Cell Count and Differential*

	BEFORE TREATMENT WITH ACTH	DURING TREATMENT WITH ACTH
Average total WBC per cu. mm.....	8,800	15,800
Average absolute number of segmented neutrophils.....	5,180 (60%)	14,062 (89%)
Average absolute number of non-segmented neutrophils.....	176 (2%)	316 (2%)
Average absolute number of lymphocytes.....	2,943 (34%)	1,393 8.5

hormone there occurred a very considerable increase in the total peripheral white blood cell count, due mostly to the marked increase in both the percentage and total number of polymorphonuclear leukocytes (table IV). With this there occurred a reduction in the absolute number of circulating lymphocytes. These results are similar to those reported originally by Dougherty and White in the rat (5), and by Thorn, Prunty, and Forsham (6) in a patient with mild pituitary insufficiency who was treated with adrenocorticotrophic hormone. Mason and his group failed to confirm these findings in a normal woman injected with this hormone (4).

*The Effect of Adrenocorticotrophic Hormone on the Symptoms of the Patient, the Daily Prostigmine Requirements, and the Size of the Mediastinal Mass.* Prior to the administration of adrenocorticotrophic hormone the daily prostigmine requirements of the patient did not vary significantly with changes in the daily



salt intake. During the early salt deprivation periods it appeared as if the patient were somewhat more uncomfortable on a salt-free diet than when the daily salt intake was increased to 8.0 Gm. This observation, however, was equivocal and was not reflected in any change in the daily prostigmine requirement. The withdrawal of the drug during either period resulted in a marked exacerbation of the symptoms. The size of the tumor was unaffected by the daily intake of salt.

After 4 days of treatment with adrenocorticotrophic hormone a roentgenogram of the chest showed a marked decrease in the size of the mediastinal mass as compared with all previous x-ray examinations (figs. 1 and 2). The last control roentgenogram of the chest was made directly before the treatment with the hormone was begun. The mass remained considerably reduced in size for 2 weeks after cessation of therapy and then began to increase. By the end of the third week after therapy had been discontinued the mass had again attained its original size.

During the period of observation the heart did not change in size. However, before treatment with ACTH an electrokymogram of the left ventricular border<sup>6</sup> showed unusual deviations from the normal pattern. At the left ventricular apex, and particularly posteriorly (fig. 3), there was systolic expansion. This was the extreme expression of the less marked changes present elsewhere. Thus, at the upper left ventricular border systolic contraction was delayed and step-like. More inferiorly, the ventricle moved mesially in the isometric phase of systole, then moved laterally to be followed by complete systolic ejection beginning 0.05 sec. after the major rise of the carotid pulse tracing and 0.18 sec. after the onset of the QRS complex. After treatment with the hormone the electrokymographic tracing returned to a more normal pattern. The ejection was still somewhat unusual, however, and consisted of a mesial movement commencing at the onset of the isometric systolic phase, a slight halt and lateral movement, and followed, in 0.02 to 0.03 sec. after the major rise of the carotid pulse tracing, by the completed ejection.

During the period of treatment with adrenocorticotrophic hormone there was no change in either the patient's symptoms or the daily prostigmine requirements. Three or four days after therapy was discontinued, however, the patient began to experience an increase in the sense of well being and an increase in strength. The daily need for prostigmine became progressively less, and for the last two weeks (that is, 32 days after completion of therapy with adrenocorticotrophic hormone) she has required no prostigmine at all. This period represents the first in 4 months that the patient has felt perfectly well without the aid of prostigmine. The improvement in her clinical symptoms has continued to date, which is 46 days after cessation of therapy with adrenocorticotrophic hormone. It is interesting to note that although the tumor has now attained its previous size there has as yet been no recurrence of the myasthenic symptoms although such a recurrence is to be expected. It is important to observe the lag that

<sup>6</sup> The electrokymographic tracings were made by Drs. S. Daek, D. H. Paley, and M. L. Sussman.

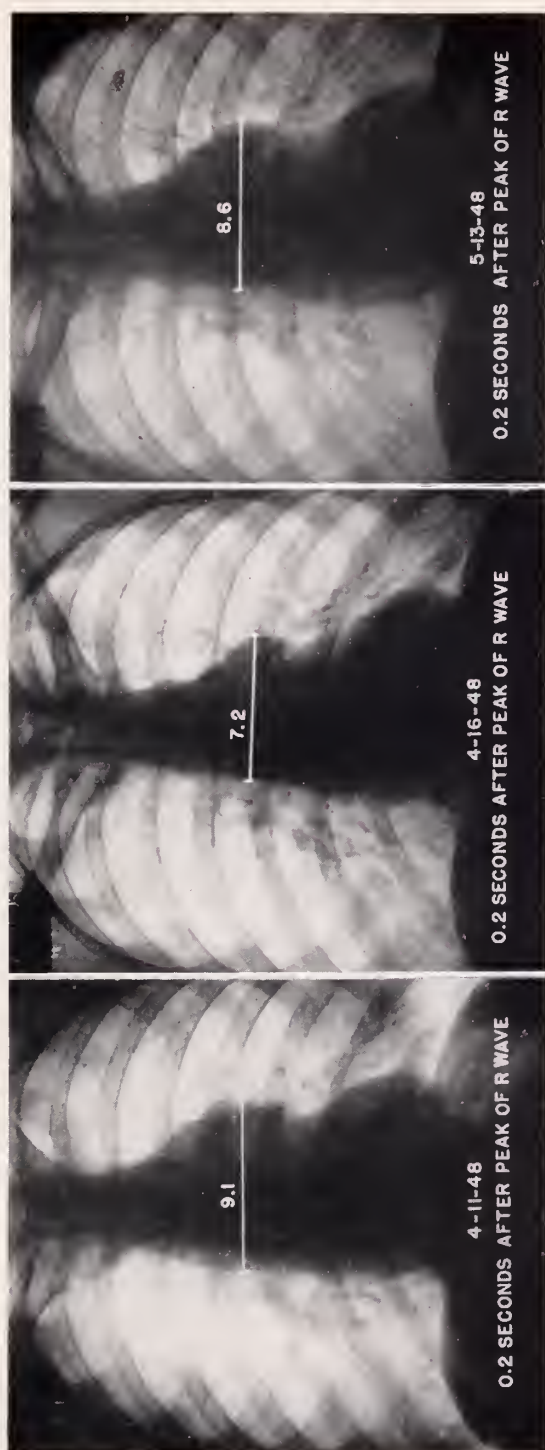


FIG. 1. Roentgenograms made during the same phase of the cardiac cycle (mid-systole) and respiration.

4-11-48 Before treatment with ACTH  
 4-16-48 Immediately after completion of treatment with ACTH  
 5-13-48 4 weeks after completion of treatment with ACTH

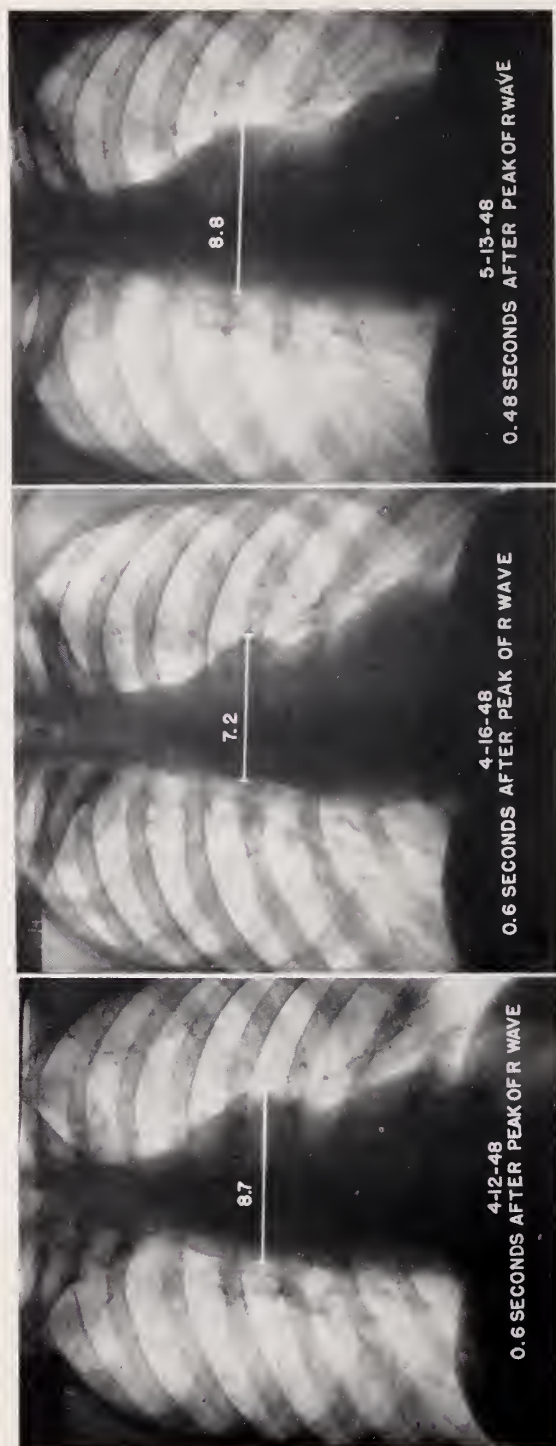


FIG. 2. As Figure 1, but roentgenograms made during diastole

occurred between the decrease in size of the tumor and the improvement in the clinical symptoms.

It is possible that the beneficial effect of adrenocorticotrophic hormone on the size of the tumor may be due to the dissolution of thymic lymphocytes which follows the injection of this hormone in the presence of intact adrenals.

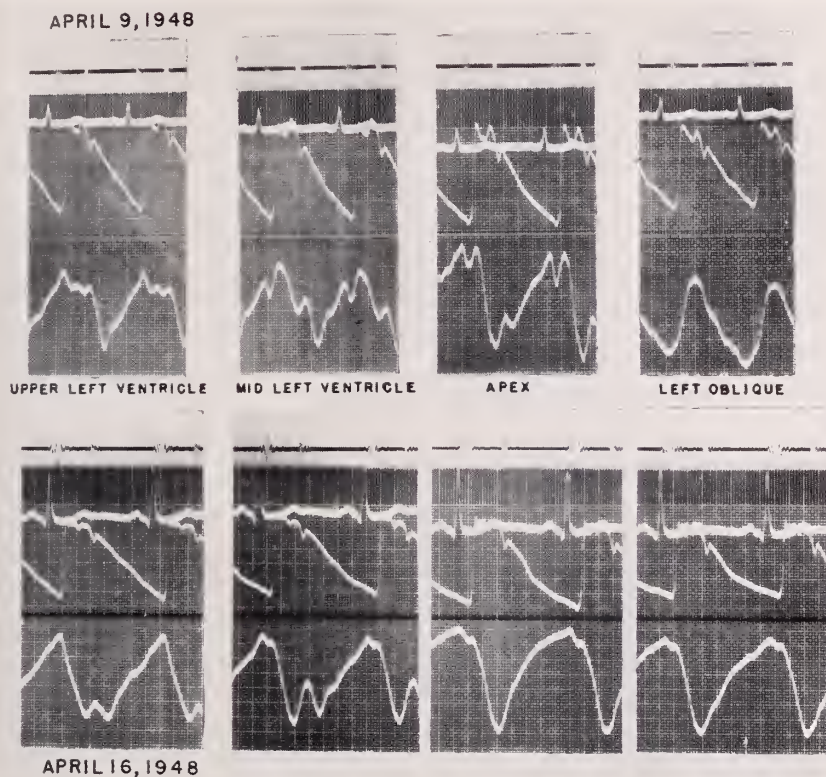


FIG. 3. Simultaneous recordings (from above down) of the heart sounds, Lead II of the electrocardiogram, carotid pulse wave and the electrokymogram. The latter were recorded over the contour of the upper, mid, apex, and posterior apex of the left ventricle.

4-9-48 Before treatment with ACTH

4-16-48 Immediately after completion of treatment with ACTH

If this is so, then the administration of carbohydrate fractions from the adrenal cortex should produce similar results. Actually, a similar although less pronounced reduction in the size of the thymic mass followed the daily administration of 5 cc. of lipo-adrenal extract (Upjohn) 3 times a day for 4 days.

#### SUMMARY

1. The administration of 40 mg. of adrenocorticotrophic hormone daily in 4 divided doses for 4 days to a patient with myasthenia gravis with a thymic tumor resulted in a marked decrease in the size of the tumor, a marked improve-



ment in the clinical symptoms, and elimination of the daily necessity for prostigmine.

2. The decrease in size of the tumor lasted for approximately 3 weeks, by the end of which time it regained its previous size.

3. The improvement in symptoms has continued to the time of this writing, which is 46 days after 4 days of therapy with adrenocorticotrophic factor was completed. During this period of time there has been a progressive reduction in the daily requirement of prostigmine, and during the past 2 weeks none at all has been required. It is not expected that the clinical improvement will continue indefinitely.

4. The adrenocorticotrophic factor resulted in some decrease in the urinary excretion of water, sodium, and chlorides. Fluid retention and hemodilution were observed.

5. This hormone caused a marked increase in the urinary excretion of neutral 17-ketosteroids and of 3-keto- $\Delta_4$  pregnene compounds.

6. Following the injection of adrenocorticotrophic hormone there occurred a very slight decrease in the urinary excretion of creatine and a marked reduction in the excretion of creatinine.

7. The administration of this hormone was followed by a considerable increase in the total white blood cell count, due essentially to a marked increase in both the percentage and absolute numbers of polymorphonuclear leukocytes. In addition, there was a reduction in the absolute number of lymphocytes.

We wish to extend our thanks to Dr. John Bookman for his help while the patient was on the Metabolism Ward.

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## VAGOTOMY

### HISTOPATHOLOGICAL OBSERVATIONS ON THE INFRADIAPHRAGMATIC PORTION OF THE VAGUS NERVE, TEN TO FIFTEEN MONTHS AFTER SUPRA- DIAPHRAGMATIC VAGOTOMY FOR PEPTIC ULCER\*

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Although physiological changes following vagotomy have been reported, histopathological studies of the subdiaphragmatic portion of the vagus nerve following a previous supradiaphragmatic neurectomy in humans are not available. It is said that the preganglionic fibers of the autonomic nervous system possess a remarkable regenerative capacity. Gardner, Stowell and Dutlinger offer convincing proof that preganglionic parasympathetic fibers can regenerate. In a patient with petrosal neuralgia, tearing of the involved eye ceased after section of the greater superficial petrosal nerve. A complete return of tearing occurred in four months. This function was obliterated by a subsequent resection (1). Division of the cervical sympathetic trunk in experimental animals is followed by regeneration within a month despite the transplantation of the ends into opposite sides of the sternomastoid muscle (2). Tower and Richter performed preganglionic sympathectomies in cats and demonstrated by testing skin resistance, galvanic skin responses and sweating patterns, a return of normal function after periods of three to seven weeks (3). Haxton, in a clinical study of regeneration following sympathectomy, thought that the return of sudomotor and vasoconstrictor activity in denervated extremities was due to regeneration of the divided fibers. He found a period of complete absence of sympathetic activity for periods of three to eighteen months after sympathectomy to be followed by a gradual return of function in nearly every patient (4).

Information concerning the regenerative potentiality of the vagus nerve is of particular significance when ultimate results of gastric neurectomy are considered. Accordingly, segments of the vagus nerve removed from the infradiaphragmatic portions of the esophagus ten, ten and fifteen months, respectively, after a previous supradiaphragmatic resection were subjected to histopathological study. The recurrence of symptoms in these patients led to reexploration and a second resection of the vagus nerve distal to the former site of excision. These segments were subjected to histological studies. A large number of segments of the vagus nerve removed from the same region in the course of primary vagal resections were used as controls. Sections of the biopsied material were stained with hematoxylin and eosin and the Nissl methods in order to study nuclear structures; with the Weil method to demonstrate myelinated fibers; with the Marchi method

\* From the Laboratory of Neuropathology and the Surgical Service of Dr. Ralph Colp of The Mount Sinai Hospital, New York.

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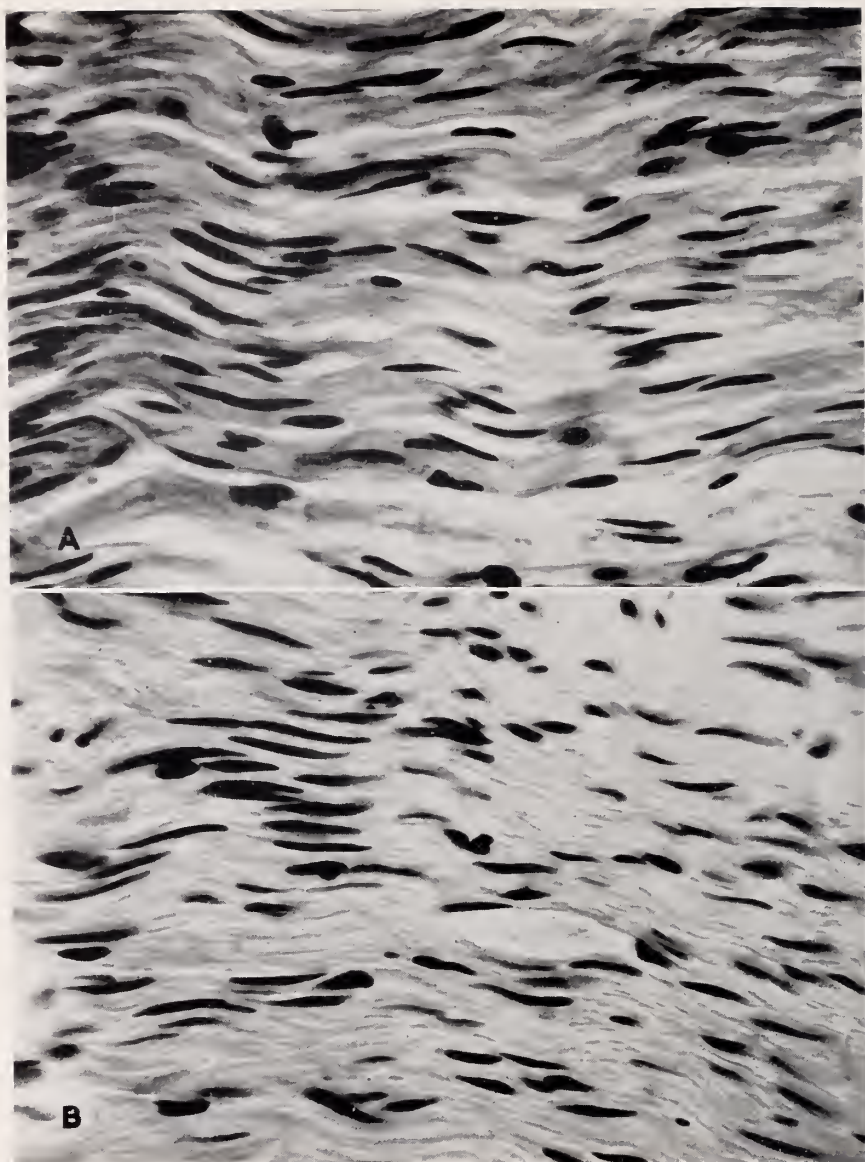


FIG. 1a. The histologic structure of the infradiaphragmatic vagus nerve (normal control). (Hematoxylin and eosin stain,  $\times 750$ )

FIG. 1b. The histologic structure of a resected portion of the infradiaphragmatic vagus nerve ten months after a previous supradiaphragmatic section. (Hematoxylin and eosin stain,  $\times 750$ )

to reveal evidence of degenerative changes and with the Davenport method to study axis cylinders.

Study of the histological preparations disclosed that the segments removed ten and fifteen months after a previous vagotomy could not be distinguished from the

control group. There were no alterations in the arrangement and number of nuclei in the endoneurium and in the Schwann cells (fig. 1). Sections stained by the Weil method revealed a few, well medullated fibers of the caliber usually seen in this portion of the vagus trunk (fig. 2).

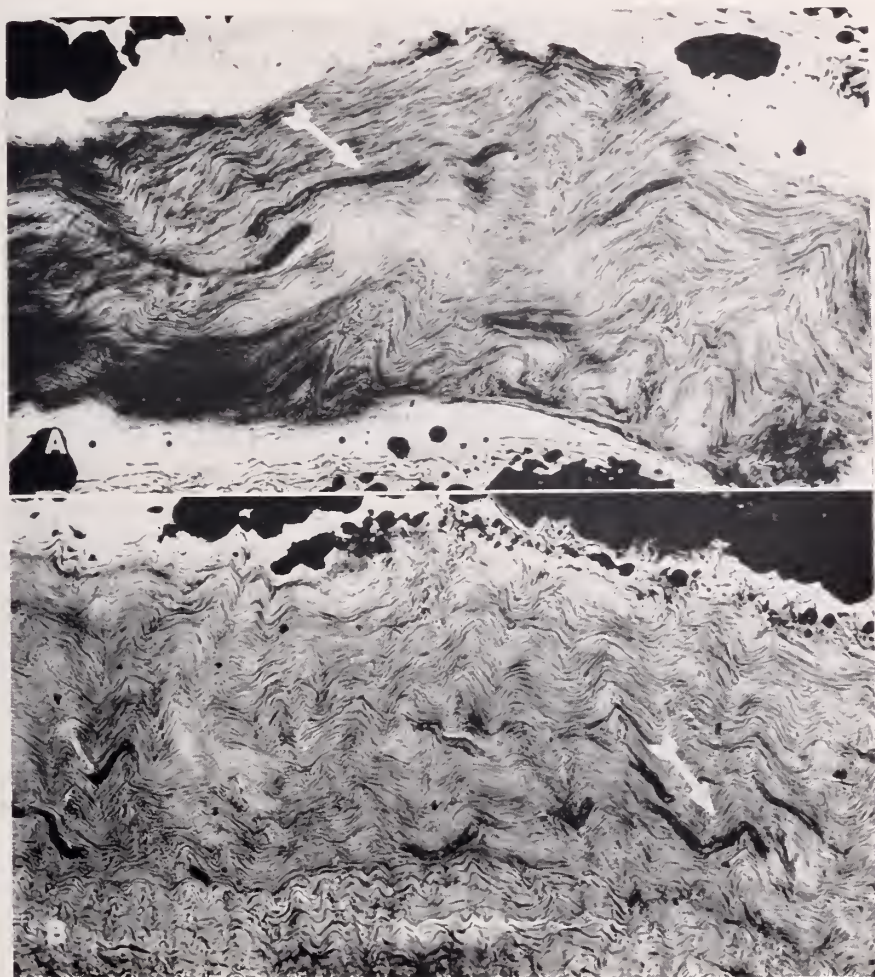


FIG. 2a. The histological structure of the infradiaphragmatic vagus nerve showing myelinated fibers (normal control). (Weil-Marchi stain,  $\times 150$ )

FIG. 2b. The histological structure of a resected portion of the infradiaphragmatic vagus nerve ten months after a previous supradiaphragmatic section. Several myelinated fibers are seen among the numerous unmyelinated fibers. (Weil-Marchi stain,  $\times 150$ )

Silver stained preparations disclosed numerous thin and delicate axis cylinders that in no manner differed from those in the control series (fig. 3). Sections stained with the Marchi method revealed no evidence of secondary degeneration (fig. 2). Since the surgical specimens were removed ten to fifteen months after the initial resection, sufficient time had elapsed during which the products of



degeneration could have been completely removed. The material which was studied as thoroughly as possible disclosed islands of well preserved nerve fibers.



FIG. 3a. The histological structure of the infradiaphragmatic vagus nerve showing numerous axis cylinders (normal control). (Davenport stain,  $\times 225$ )

FIG. 3b. The histological structure of a resected portion of the infradiaphragmatic vagus nerve ten months after a previous supradiaphragmatic section. Numerous axis cylinders are seen. (Davenport stain,  $\times 225$ )

These fibers showed no differences from similar normal nerve structures, manifesting no evidence of degeneration or regeneration.

It was of interest that the second, infradiaphragmatic resection failed to alter

the positive insulin test and resulted in no significant improvement in the patients' symptomatology.

#### DISCUSSION

The preganglionic fibers of the vagus nerve form autonomic plexuses in the walls of the viscera before terminating by synapsing with the cells of origin of the postganglionic fibers. At its exit from the skull, the vagus nerve contains large and small fibers. The former innervate chiefly the pharynx and larynx. Those supplying the esophagus and the stomach consist of non-medullated fibers, of small medullated fibers and a considerable number of medium, but hardly any large medullated fibers (5).

McSwiney and Spurrell are more specific in their views concerning the number and distribution of myelinated fibers of this nerve in the cat. They found that the bulbar roots of the vagus and its trunk above the ganglia contain predominantly medullated fibers, both small and large. Below the ganglia a large number of non-medullated fibers appear with the majority of medullated fibers leaving the parent trunk to form the pharyngeal and laryngeal branches. The proportion of non-medullated fibers increases in the thoracic portion of the trunk until finally the abdominal branches consist almost entirely of non-medullated fibers. They concluded that the bulk of the fibers to the stomach leave the medulla with myelin sheaths and reach the stomach as non-medullated fibers. The loss in myelination apparently occurs in the vicinity of the jugular and nodosal ganglia (6).

Gaskell also points out that many non-medullated fibers are present in the vagus immediately below the ganglia. It is his opinion that efferent, preganglionic fibers passing without interruption in the ganglia lose their medullary sheaths at some point in their course toward their termination (7). Faley and Du Bois, in the most recent quantitative analysis of the efferent and afferent fibers of the vagus nerve in the cervical region of the cat, conclude that sensory fibers constitute from 65 to 80 per cent of the total number, the remaining 20 to 35 per cent being motor, efferent fibers. Only 23 to 33 per cent of the fibers are myelinated. This includes 10 to 20 per cent of all sensory fibers and 48 to 71 per cent of all motor fibers. As determined by actual count, more than two thirds and in some instances three fourths of the afferent fibers are of the smallest variety. In addition to a moderate number of slightly larger fibers, these two types constitute 75 to 80 per cent of the total number of afferent fibers, a figure which compares closely with the 80 to 90 per cent of unmyelinated fibers found in the right vagus nerve. The authors, therefore, propose that myelination is based on the size of the axons, the vagal sensory fibers being preponderantly unmyelinated because of their preponderantly small diameter (8). Although fiber counts could not be made in the present investigation, the evident paucity of medullated fibers in the terminal esophageal and gastric portions of the vagus nerve is in conformity with these observations.

The return of autonomic function following regeneration of the fibers of the vagus nerve is still in doubt. In an experiment on a cat twelve months after



vagus section, the peripheral end was stimulated and produced no demonstrable effect. Histological examination, nevertheless, showed that the nerve had largely regenerated (5). Tsukaguchi excised 23 mm. segments from the vagus trunk in the midcervical region in each of two dogs. On stimulation of the peripheral end of the vagus 175 days after the section was performed, he was unable to obtain evidence of cardiac inhibition. Subsequent histological studies revealed the presence of regenerated fibers in the non-functioning nerve (9). Vanzant reexamined a group of dogs two years after the vagal supply to the stomach was sectioned in the thorax. An analysis of the gastric secretions revealed acid curves which were practically as high as those before operation. The return of the normal acid values was not due to regeneration of the vagus nerves as proven by subsequent autopsy (10).

It was suggested that the stomach was so nearly autonomous that although secretory functions were at first greatly altered by the removal of autonomic influences, after a time these functions could be restored. One must not ignore the mixed composition of the splanchnic and vagal trunks, each of which conveys secretory fibers to the gastric mucosa. Interruption of one trunk could only partially denervate the organ. Since both the splanchnic trunks and the vagi possess an extraordinary power of regeneration, this factor must also be considered. On the other hand, functional recovery after regeneration of the vagus nerve was proven by electrical stimulation of the cardiac fibers after the trunk had been cut or crushed in the mid-cervical region. In the rabbit, regeneration occurred three to four months after crushing and between 14 and 30 months after cutting. In the cat, regeneration of the autonomic efferent fibers was obtained seven months after crushing and 374 days after cutting. Regeneration of the recurrent laryngeal fibers of the vagus in the rabbit and cat with functional recovery of the paralyzed vocal cord was obtained and confirmed histologically (11).

Although evidence of regeneration of the fibers through the distal segment of the severed vagus nerve has been reported as a fairly constant finding, restoration of physiological activity as a result of reinnervation is still in doubt. In order to produce lasting physiological results, denervation of an extremity or viscus must be carried out in such a way that regeneration cannot take place. Following an incomplete denervation, the remaining intact autonomic fibers are capable of liberating a chemical mediator substance at their endings which stimulates the denervated—and thereby sensitized—smooth muscle cells bringing about a recurrence of the original disorder (12).

#### SUMMARY

In three patients in whom supradiaphragmatic gastric neurectomy had been performed, recurrence of the ulcers and the associated symptomatology warranted reexploration after intervals of ten to fifteen months. Histological studies of segments of the infradiaphragmatic portions of the vagus trunks removed at the second operation revealed no abnormalities when compared with a large group of control preparations.

I would like to thank Dr. Joseph H. Globus, Dr. Ralph Colp and Dr. Vernon Weinstein for their help and encouragement in the preparation of this paper.

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# OBSTACLES ENCOUNTERED IN RECOMMENDING PSYCHOTHERAPY

## A FOLLOW-UP STUDY OF 400 CASES<sup>1</sup>

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*Source of the material.* The Consultation Service of the Mount Sinai Hospital in New York is a diagnostic clinic for persons with a maximum yearly income of \$2400 if single and \$4000 if the head of a family, who pay a flat fee of \$40 for whatever tests and studies are indicated. Each patient is referred by his own physician to whom an exhaustive report is sent containing findings and recommendations. In general the physician refers his patient to the service for one of the following reasons:

a. He seeks aid in arriving at a diagnosis utilizing the opportunity provided by the service to enlist specialist's opinions and special studies at a much lower fee than would be otherwise possible.

b. He is more or less certain that his patient is suffering from a neurosis but wishes to convince both the latter and himself that nothing "organic" is being overlooked.

Naturally the second category includes a large number of psychoneurotic individuals. Yet it is also true of the first group which contains a large number of neurotic patients who have been treated erroneously in the past for Addison's disease, Graves' disease, coronary artery disease, endocrine disorders etc. As a consequence a great number of reports sent to the referring physician carry the recommendation that the patient receive psychotherapy. This study was undertaken to discover the fate of this recommendation in 400 consecutive cases. To determine this a letter was mailed to the physicians, who had referred these patients originally, inquiring whether the patient had secured psychotherapy, and if so of what nature and what duration.<sup>2</sup> A period of at least 6 months had elapsed between sending out the original recommendation and the follow-up questionnaire.

*Results.* Replies were received covering 270 individuals. In 41 instances the writer declared that he had virtually lost contact with his patient and that he was consequently unable to provide any information concerning him. It seems safe to assume, however, that these individuals, who for one reason or another failed to keep in touch with the physician who referred them for so complete a diagnostic study, would not have gone off on their own to seek psychiatric help. Of the total of 270, 19 or 7 per cent procured some type of systematic psychiatric

<sup>1</sup> From the Consultation Service of Dr. Herman Lande, and from the Neurological Service of Dr. I. S. Wechsler, The Mount Sinai Hospital, New York.

<sup>2</sup> In about one half of the cases the report to the doctor specifically advised that the patient receive psychiatric care or be referred to a psychiatrist. In the remainder the report simply recommended "psychotherapy." The latter word was also employed in the follow-up questionnaire without further definition. This seemed desirable since it offered the doctor considerable latitude in illustrating his interpretation of the term.

therapy: one patient undertook psychoanalysis; 6 others received some undescribed form of apparently long-term psychotherapy. One patient attended a mental hygiene clinic; 2 received shock therapy, and 3 were hospitalized in mental institutions. Six others were seen by psychiatrists for a total of less than 5 visits each, a program which was clearly inadequate from the problems they presented. In short, actually only 13 or less than 5 per cent of the 270 secured anything like adequate psychiatric therapy. (It is pertinent to wonder about the fate of the 130 patients whose doctors did not answer the questionnaire. In view of the lack of cooperation of the latter regarding the questionnaire, it seems unlikely that they had been successful in carrying out the original recommendation. If this assumption is correct the percentage of the total number of 400 patients receiving psychiatric therapy becomes  $3\frac{1}{4}$ ).

Two hundred and fifty-one or 93 per cent of the total number reported failed to receive any accepted or significant psychiatric therapy. The responses concerning 210 of these were grouped as follows (41 were lost track of): in 95 instances without furnishing any explanation the doctor simply stated that no such therapy had been provided; 87 patients were said to have refused such treatment for reasons other than the financial problem involved; 21 were reported to have refused the recommendation because of their inability to afford such therapy; in 3 instances, the doctor stated that he did not know to whom to refer his patient; 3 other physicians failed to extend the recommendation to the patient because they did not concur with it. One patient developed an unrelated organic illness which made the need for psychiatric therapy less evident.

Despite the lack of psychiatric therapy, however, many of the responses indicated that the patients had improved. In 13 cases no discernible reason was cited for such improvement. In 21 instances it was attributed to reassurance, explanation, advice and other forms of superficial psychotherapy. The report from the Consultation Service stating that "nothing was wrong" appeared to have helped another 20 cases. The return of service men brought relief to another 7. Marriage, pregnancy, release from burdensome responsibilities were cited as beneficial to 5 additional individuals. Three were apparently aided by "medical" measures. Vacations, intense work and so forth were held responsible for the improvement of 5 more. In sum, 74 or 36 per cent of the 210 patients who failed to receive the psychotherapy suggested for them were said to have improved for one reason or another.<sup>3</sup>

Because of these claims it seemed appropriate to review the records of these patients in an attempt to evaluate the significance of their reported improvement. (It was not practical to re-examine the patients.) A few examples are presented:

<sup>3</sup> It might be argued that these patients actually did receive psychotherapy in terms of reassurance, encouragement and so forth. Granting this, however, it must be stressed that in very few instances did the doctor's efforts seem to warrant such a designation. Rarely was there a hint that any attempt had been made to deal with the psychologic material underlying the neurotic picture. Viewed in this light there is little reason to suppose that the "reassurance, encouragement etc." would have any more lasting effect on these patients than on any others.



*Case 1.* A 40 year old married woman who had been complaining of rectal cramps and diarrhea for two years. She also suffered from attacks of trembling of the legs, frontal headaches, nausea, insomnia, nervousness, palpitations and globus. When her husband was a little delayed in coming home she became unduly agitated. In answer to the questionnaire her doctor reported tersely: "— received no further treatment. *She is completely cured.*"

*Case 2.* A 41 year old single man had suffered from chronic constipation, nervousness, coldness of the extremities, easy fatigue, dizziness on bending over, palpitations and excessive sweating for some 10 years. He was described as self-centered, irritable, perfectionistic, ambitious and over-attached to his mother. He had never married because he had never found a woman who was good enough for him. His doctor reported: "No psychotherapy was provided for the patient. He only took a vacation in the country and returned greatly improved."

*Case 3.* This 44 year old man was a severe agoraphobe. He became frightened while in bed at night and was subject to spells of choking and globus. For four years he had been suffering from headache, and various other complaints. His doctor stated: "*Fully recovered.* When he found out there was no organic trouble, it seemed to relieve his mental condition."

*Case 4.* A 34 year old man had had a "nervous breakdown" eleven years before. Since that time he had been subject to attacks of shaking and fearfulness. He was unable to ride in the subways or walk past funeral parlors. There was a long story of agoraphobia and claustrophobia. Moreover he was depressed and subject to post-prandial epigastric fullness. After defecation he felt burning pain rectally. There were frequent nightmares, often involving rats fighting. He gave the impression of being suspicious and mildly paranoid. His doctor wrote: "He has improved so much with medical care for his nervous stomach ailment that he has gradually dropped all his phobias. This treatment acted as a psychotherapy. *He is now a normal man.*"

One can hardly read these reports without being moderately startled by the subsequent glowing reports of the referring physician. To learn that treatment for a nervous stomach, for example, successfully cured a somewhat paranoid individual of multiple complaints including agoraphobia and claustrophobia of 11 years' duration, taxes one's credulity. Yet there is no reason to question the good faith of either this physician or of the others who wrote somewhat similar reports. One must conclude that the patient was improved (if not a "normal man") and that this improvement was related to the treatment he received, whether through suggestion, gratification of unconscious wishes, the feeling that someone was protecting him and giving him attention or what not.

At the same time psychiatrists who are familiar with the usual fate of such phobias, for example, will question how well this doctor knows his patient, how much the patient has reoriented his life in order to avoid phobia-producing situations, how permanent will be his relief, and finally what is meant by a "normal man." Every psychiatrist is familiar both with the fluctuations of neurotic symptomatology and with their susceptibility to various influences both beneficial and detrimental. Knowledge of the deep seated meaning and language of the neurosis, therefore, permits one to qualify the significance of the reports of marked improvement in 36 per cent of untreated neurotic individuals. Further, such reports should not be permitted to discourage the application of proper and scientific psychiatric therapy to those individuals who are neurotically ill.

*The patient's attitude.* In view of such apparent improvement it is not hard



to understand the reluctance of either the patient or his physician or both to follow the recommendation of the Consultation Service that the patient undertake psychotherapy. However, in a large number of instances—87 out of 210—the doctor reported that the patient refused psychotherapy, and not out of financial considerations. Such a claim is of no small importance since it indicates that in this group of individuals, at least, financial limitations alone do not provide the major obstacle to the attainment of psychiatric therapy. It seems more than likely that many psychoneurotic individuals are already proclaiming their resistance to psychotherapy by allowing themselves to undergo a long and searching work-up such as is furnished at the Consultation Service. This is especially obvious in phobic and compulsive individuals whose somatic symptomatology is relatively meagre and whose attendance at a diagnostic clinic is motivated by a hope that some organic derangement will be found which will provide them with a further defense against facing their keenly perceived psychologic suffering.

*Case 5.* A 28 year old woman had attempted suicide at the age of 14. She was obsessed by fears of what she might do to herself and others in her sleep. She could visualize herself doing "terrible things" to offset which, she indulged in rituals. When she slapped her dog she developed severe anxiety symptoms. Her doctor reported that she had rejected all the psychiatrists he had recommended which is hardly surprising in an individual who has submitted such patently psychiatric problems to a medical diagnostic clinic.

Resistance to the acceptance of the need for psychiatric help in other patients was manifested by a refusal to acknowledge the existence of any emotional problems, and an insistence on the "organic" nature of their suffering.

*Case 6.* A 38 year old woman complained of pain in both breasts. In addition she suffered with pain in the epigastrium, insomnia, palpitations, sighing respiration, globus and nausea. She felt "liquid running through her legs." During the basal metabolism test she felt she would suffocate. Her defensive attitude toward her symptoms was exhibited by her describing her pains as "not imaginary", "definite", although her sincerity had not been questioned. Her physician reported: "Psychotherapy has been refused by the patient and her mother."

Another group of patients who offer resistance to psychotherapy comprises those battle-scarred individuals who are repeatedly subjecting themselves to surgery, motivated by a variety of reasons including guilt, atonement, masochistic pleasure etc. In collusion with an over-exuberant surgeon, it is almost inevitable that sooner or later there will be another laparotomy.

*Case 7.* A 30 year old single woman complained of pains all over and "dizziness" after eating. She was subject to repeated sore throats and weak feelings. Her marriage had terminated in divorce after 1 year. She had sprained her ankles repeatedly. One and a half years ago she was said to have suffered a cerebral concussion after hitting herself on the head with a tennis racket. Her doctor wrote: "She refused psychotherapy. Instead somebody persuaded her to have her appendix removed."

*Case 8.* A 50 year old woman complained of weak feelings and a fear of falling over a long period of time. There had been transient episodes of inability to speak as well as attacks of numbness throughout the left side of her body. She was harassed by "pains all over." In the course of 25 years she had had 5 major operations. Five years before she had been confined to bed for 22 weeks because of a "nervous breakdown." She was subject to classical anxiety symptomatology. Psychotherapy was advised. Her doctor wrote, however,

that "subsequent investigation showed the patient to be suffering from gall bladder disease. A cholecystectomy was performed. Patient did not receive psychotherapy."

*Financial limitations* was offered as the reason to reject psychotherapy in 21 instances, (10 per cent of the refusals). The validity of this explanation apparently varied from case to case, some doctors claiming that the patient was simply using this as an excuse. Other physicians wrote that they knew of no psychiatrist whose fees would be met by their patients. In actuality, financial limitations constitute a very real obstacle to the attainment of adequate psychotherapy, so that there is a bit of hypocrisy in recommending psychotherapy to people who couldn't afford it if they wanted it. Yet it is striking that in 90 per cent of the refusals this reason was not adduced, leading to the conclusion that in this group of patients at any rate, the resistance to psychotherapy by themselves (or their doctors) precedes financial considerations.

*The doctor's attitude.* In 3 instances the doctor was candid enough to state that he did not concur in the recommendation. In other instances it is evident that the recommendation was plainly ignored. On the other hand the replies of other physicians revealed an awareness of the problem of psychotherapy both from the point of view of the patient's resistance and the socio-economic aspects. One wrote: "Although she could work to cover costs she said she couldn't afford it." Another stated: "She continued her usual round of physicians in search of the miracle cure." Some of the replies indicate that the doctor made strenuous efforts to explain the indication for psychiatric therapy to the patient as well as to refer the patient to specific psychiatrists.

Doubtless the attitude of the physician who recommends such treatment will play a crucial role in determining the outcome. There is an important difference between a painstaking exposition of the problem to the patient which is accompanied by a list of reputable psychiatrists and a cavalier attitude of "Well, there's nothing wrong with you. The report says it's all in your mind. Maybe you ought to see a psychiatrist." Whereas the replies received do not indicate what effort was expended by the physician in the matter, the impression was often conveyed that his own lack of understanding, awareness, and sympathy militated against success. The language employed often fails to reflect even the simplest understanding of psychiatric illness. Some writers do not seem to have a clear knowledge of the difference between psychiatry and neurology. Others imply that psychogenic illnesses are imaginary and consequently in the realm of fakery. In short, the conclusion is inescapable that the failure to provide psychotherapy for more than 95 per cent of 270 neurotic patients—leaving aside financial considerations—cannot be ascribed entirely to the resistance of the patients. The doctor too has his resistances as well as his inexperience with the problem. Such heroic exhortations as "pull yourself together," "why don't you get a hold of yourself?", "you're just talking it into yourself" and other expressions designed to spur the patient into mental gymnastics of a totally meaningless nature attest to the fact that the doctor is often totally unqualified to recommend psychiatric therapy, let alone administer it.

*Situational obstacles.* The responses of several physicians reflect an awareness

of the greatest obstacle to the recommendation of psychotherapy, namely, the shortage of available psychiatrists and clinics and the huge expense involved:

"None available for her at her income level."

"First the patient is unable to pay a specialist's fee, and second I do not know where and to whom I might send him for clinic treatment or for a nominal fee. Should you have such a department or have any suggestions along these lines, I would be pleased to hear from you. Any suggestions will be greatly appreciated."

"This patient did not get psychotherapy. There is not a psychiatrist that I know of in this entire county of one half million people (Nassau) that I can refer any patient with any degree of satisfaction as regards psychotherapy. This is also the experience of fellow general practitioners and it is really a shame."

"In answer to your recent letter regarding psychotherapy for Mrs. X., I regret to state that the patient was unable to afford such treatment. If I may add my opinion on the matter of the availability of psychiatric therapy to the public, it has been my experience that a large number of individuals coming to see an internist are in need of such therapy. Unfortunately, there are too few qualified psychiatrists, making appointments difficult to obtain. In addition, a very large proportion of those who need such therapy are utterly incapable of paying the private fees which are current."

"His financial position would not warrant such attention at the usual fees. The care he would obtain at a clinic under present conditions would, in my opinion, be of doubtful value. If you are planning to set up facilities to administer good psychiatric care to people of limited means, I would be very much interested to be advised of this."

These statements, unfortunately, truthfully reflect the virtually impossible task of providing certain individuals of limited means with adequate psychiatric help. Psychiatrists in private practice can see but a limited number of patients, charge high fees and are obliged to turn away patients today regardless of their ability to pay simply because of time limitations. Mental hygiene clinics are few in number, tend to be overcrowded, and often provide mediocre treatment. Consequently even if the obstacles already cited were lessened, the lack of adequate private or clinic facilities makes of the recommendation for psychotherapy a hollow mockery—like encouraging an impecunious ward patient to take an ocean cruise during a maritime strike.

This study provokes a challenge. It indicates that less than 5 per cent (probably more likely  $3\frac{1}{4}$  per cent) of a group of patients were furnished with the psychiatric help which was suggested for them. This outcome is apparently due to 3 separate factors: 1. The resistance of the patient to the idea of undertaking psychiatric therapy. 2. The lack of cooperation or understanding on the part of the medical practitioner. 3. The lack of psychiatric facilities to meet the needs and financial capacities of the patient. Each of these factors constitutes a separate problem, yet the solutions involved tend to overlap in some sense. The attitude of the public toward psychiatry and psychiatric illness is partly capable of being influenced through educational and other channels. Articles in the popular weekly magazines on "Psychosomatic Medicine" have reached

a wide circulation. Undoubtedly Alfred Hitchcock's *Spellbound*, and Moss Hart's *Lady in the Dark* may contribute some degree of insight for a small segment of the population and serve to ameliorate the stigma of neurosis, but in general the public does not differentiate too well between neurosis and psychosis and the movies have done little to dispel the idea that the neurotic is a "screwball", to say nothing of the psychiatrist, who in one recent film turned out to be the villain of the piece. Granted that sometimes the most psychiatrically-minded individuals can display the most potent resistance to the advice that they seek psychiatric help, greater enlightenment concerning the aims and goals of modern psychiatry could do much toward lessening the barrier which so many individuals erect against recognizing any emotional determinants of their suffering.

The doctor's attitude is compounded of the same factors just cited modified by whatever influence his psychiatric training in medical school may have had. Too often the latter is grossly inadequate and concerns itself more with the phenomena of grandiose delusions, auditory hallucinations, and disorientation than with the problem of anxiety and its ramifications and the manifold defenses erected to combat it. The time has passed when a combination of palpitation, cold moist hands, sighing respiration, insomnia and so on should be termed "autonomic imbalance."

Granted, however, that an enlightened public will more willingly accept the recommendation of psychiatric therapy proffered by a more psychiatrically oriented physician, profound changes will be necessary to render that therapy available. It has been estimated that whereas one half of the medical care which ambulatory persons need is ultimately psychiatric in nature, there is but one psychiatrist to every 65 practitioners.<sup>4</sup> It has been the growing awareness of this problem as well as other aspects of the general question of the care of the mentally ill which has lately given rise to Federal legislation and other efforts to deal more effectively with the all important question of the physical and mental health of the nation.

The writer is indebted to Marjorie S. Cohn, Secretary of the Consultation Service for her invaluable assistance in making this study possible.

<sup>4</sup> It is not implied that every psychiatric problem must be dealt with by a psychiatrist. A recent experimental teaching program at the University of Minnesota indicates what can be done to make of the general practitioner a psychotherapist equipped to handle at least some neurotic problems with more than simple reassurance and encouragement.



## PROTRACTED COURSE IN PERIARTERITIS NODOSA\*

FREDERICK H. KING, M.D.

This case is described for several reasons: first, because its clinical course is much longer than usual; second, because it illustrates at once the difficulty and yet the possibility of making the diagnosis when the common clinical manifestations are absent and third, because it serves as a point of reference for discussion of the patho-genetic nature of the disease.

### CASE REPORT

This patient, a woman, aged 51, had a long medical and psychiatric history. As far back as 1938 she was attending the Out Patient Department of The Mount Sinai Hospital, where she was treated for psychoneurosis, a condition which has colored her illnesses and perhaps delayed appreciation of their gravity. At about this time she was also suspected of having gall-bladder disease, although x-ray studies of the gall-bladder were negative. In 1940 she began to suffer with chronic sinusitis and was being treated in the nose and throat clinic. At this time she was having asthmatic symptoms and was therefore also attending the asthma clinic. On the presumption that the chronic pansinusitis was the underlying factor responsible for the asthma a sphenoethmoidectomy was advised, which the patient refused. In the subsequent 3 or 4 years both of these conditions remained unrelieved. In 1941 she developed arthritic symptoms affecting her hands and feet; and again it was thought that the causative focus of infection was in the sinuses.

It was not until March 1944 that the patient finally accepted the advice of the rhinologists and was admitted to the nose and throat service for sphenoethmoidectomy and intranasal antotomy. As adjuvant therapy to the nasal operation she was given two courses of sulfathiazole. During the first she received 24 Gm. of the drug in 3 days, and during the second, 12 grams in 2 days. There were no manifestations of hypersensitivity. The diagnoses listed on discharge were (1) chronic polypoid pansinusitis, (2) allergic rhinitis, (3) rheumatoid arthritis and (4) psychoneurotic personality. In the light of the subsequent history, it is significant to note that she had a blood pressure of 120, systolic, and 70, diastolic. The blood count showed a slight secondary anemia. The white blood and differential counts were relatively normal except that she had a somewhat increased number of eosinophiles—7 per cent and 8 per cent. The urine did not show any abnormalities.

One month after her discharge from the nose and throat service she was admitted for the first time to the medical service. The sphenoethmoidectomy had not yet beneficially affected her asthma and the arthritis had become worse. Her functional complaints had been enhanced by aggravation of her husband's cardiac status. All her joints, both large and small, were painful on motion. The interphalangeal joints were spindle shaped and the skin over them was tight and glassy. The knees showed similar changes. She continued to be over-anxious, emotionally labile and hypochondriacal. There was, however, no fever, hypertension, urinary abnormalities or eosinophilia. Her antra were irrigated. She was seen by a psychiatrist who advised her return home for ambulatory care of her organic complaints and for psychotherapy.

Within 2 months after her discharge she was again in the hospital. This time as a private patient to be treated for the rheumatoid arthritis. She was given 6 injections of typhoid vaccine in a 2 week period in doses increasing from 2.5 million to 15 million typhoid bacilli. There followed little improvement. On this admission she again had no abnormal urinary findings, or hypertension. However, she still had 7 per cent eosinophiles.

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\* Presented at the Clinical Conference, The Mount Sinai Hospital, New York, November 17, 1947.



Four months after discharge she was admitted to the Montefiore Hospital with the same complaints. At this time it became clear that some other condition besides her previously diagnosed illnesses was present. She showed a marked eosinophilia, varying from 25 per cent to 43 per cent. Sternal puncture also disclosed eosinophilia but there was no evidence of a blood dyscrasia. Smears from the nasopharyngeal mucosa revealed the presence of eosinophiles in abnormal numbers. Stool culture was negative for ova and parasites, typhoid, paratyphoid or dysentery. The trichinella skin test was negative. The diagnostic possibility of periarteritis nodosa was considered. Because of this a muscle biopsy was done, which, however, disclosed no abnormality.

The patient came under observation at The Mount Sinai Hospital about 5 months after she left the Montefiore Hospital. She had been febrile at intervals during the antecedent few months. She had also lost a great deal of weight, in all 40 pounds in the preceding 1 to 1½ years. The presence of upper abdominal discomfort, punctuated with acute attacks of pain radiating toward the right and the back, prompted her physician to x-ray the gall-bladder. This disclosed evidence of calculi. She was advised that her gall-bladder probably constituted a focus of infection which accounted for her recurrent fever and persistent weight loss. It was further contended that cholecystectomy offered a possibility of beneficially influencing the rheumatoid state.

The patient entered the Consultation Service for a complete evaluation of her status. Here it was noted that she had fever and a markedly accelerated sedimentation time (12 min.). There was also present an eosinophilia of 54 per cent. The blood pressure was 110 systolic and 70 diastolic, the fundi were negative and there were no important formed elements in the urine. Because of the possibility of diffuse vascular disease a search was made for skin nodules. One was found in the upper third of the left ulnar region and was removed for histologic examination. The biopsy specimen was described by Dr. Klemperer as showing "subcutaneous tissue with collagen necrosis and nodular histocytic proliferation suggestive of rheumatoid arthritis."

It was believed at the Consultation Service just as at the Montefiore Hospital that the most probable cause of the eosinophilia was diffuse vascular disease. However, there seemed insufficient evidence for the diagnosis especially in the absence of renal involvement, hypertension, fundus changes or confirmatory biopsy findings.

The patient was too ill to be further studied at the Consultation Service and she was referred for further observation to the second medical service.

Here the patient continued to complain of cramplike epigastric pain, radiating toward the back and there was slight tenderness in the right upper quadrant. She was mildly febrile, the temperature ranging from 100 to 101°F. There were marked rheumatoid arthritic deformities of hands, knees and heels. The blood continued to show marked eosinophilia (52 per cent), with a blood dyscrasia largely excluded by bone marrow examination.

It was believed by Dr. Snapper that the patient had periarteritis nodosa. However cholecystectomy was deemed advisable by him because he felt that disease of the gall bladder and cholelithiasis more than periarteritis nodosa explained the larger part of the patient's symptoms.

Accordingly a cholecystectomy was performed by Dr. Gordon Oppenheimer. The gall bladder was small, contained many small, soft, faceted pigment cholesterol stones. The external surface was smooth and no abnormal vessels were noted grossly. The microscopic examination, however, showed the typical vascular changes of periarteritis nodosa.

The patient made an uneventful recovery and was discharged on the sixth postoperative day. During the two years since her last discharge the patient has been seen on several occasions. She has improved generally. Her weight has increased from 93 to 129 pounds. She has remained afebrile for almost a year. Nevertheless, she has continued to exhibit evidence of continued disease, characterized by eosinophilia which has at various times been 53 per cent, 30 per cent and 40 per cent, and the development of tender skin nodules. Recently there appeared a tender nodule along the course of the left superficial temporal artery. However, she has not shown evidence of renal involvement or hypertension, a feature which may help explain the prolonged clinical course.

## DISCUSSION

This patient had a fairly characteristic history of a prodromal infection viz. sinusitis, and a previous allergic state manifested by asthma. Sometime before her admission to the Montefiore Hospital the patient developed evidences of a superimposed malady, suspected but unproved until cholecystectomy disclosed it to be periarteritis nodosa. These features in the history have not been unusual.

The unusual feature has been the prolonged duration of the illness. Usually this is measured in weeks or months. This patient's illness has thus far lasted between 2 and 3 years. Now, there have been rare instances of prolonged remissions and a number of cases of healing, especially in patients without renal involvement (1, 2, 3, 4). However they serve to show that the prognosis need not be fatal and they emphasize the dependence of the outcome on such factors as toxemia, extent of vascular involvement and the importance of the involved organs.

This case serves one more purpose and that is as a point of reference for discussion of the etiology of the disease.

The ideas regarding etiology have been crystallized into their present state after a long series of preliminary theories failed of substantiation and had to be discarded. Suffice it to mention that the disease has been attributed to syphilis, a filterable virus, and a single toxic agent. It has even been regarded as a disease of the central nervous system.

The view that has gained ascendancy in recent years is that periarteritis nodosa is a manifestation of the anaphylactic type of hypersensitivity. Now the idea that periarteritis nodosa may be an allergic reaction is not new. It was suggested in 1925 by Gruber (5) who noted the frequent history of previous allergic manifestations such as asthma and prodromal infection, both prominent features in this patient's history.

The idea of allergic response found support in experimental demonstrations such as those of Metz (6) and Vaubel (7) who produced lesions resembling periarteritis nodosa by sensitization of animals with foreign serum or other foreign protein. The idea received its most forceful support in the recent work of Rich (8) and of Rich and Gregory (9). Rich (8) in 1942 reported 7 cases with autopsy findings. He found vascular lesions in the viscera of 5 patients following therapeutic injection of foreign serum. Four of these had also received sulfonamide. One patient received sulfonamide therapy only. None of the patients had symptoms suggestive of periarteritis nodosa before therapy. The evidence seemed suggestive that vascular lesions of this type can be manifestations of the anaphylactic type of hypersensitivity. There was in their findings no exclusion of co-incidence. Rich and Gregory (9), therefore, reproduced in rabbits a condition analogous to serum sickness and found that they could produce typical diffuse periarteritis nodosa. They concluded that the experiments demonstrated that periarteritis nodosa is a manifestation of the anaphylactic type of hypersensitivity.

In the case herein presented the patient received sulfonamides during her first

admission. There were no manifestations of hypersensitivity and the periarteritis nodosa was demonstrated approximately 6 months afterward. These features make it seem unlikely that the periarteritis nodosa in our patient is a consequence of sulfonamide sensitivity. However in view of Rich's work such a development in a manifestly hypersensitive individual cannot be entirely excluded.

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# ACUTE OSTEOMYELITIS OF THE SUPERIOR MAXILLA IN INFANTS<sup>1</sup>

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Osteomyelitis of the superior maxilla is relatively rare in early infancy, occurring generally before the second month of life. In an excellent review Wilensky (1) stresses the following features characterizing this condition: Manifestations of osteomyelitis in or about the mouth, nose, nasopharynx, and orbit; clinical evidence of a severe infection; sequestration with ultimate loss of the entire jaw, and deformity resulting from loss of bone or teeth in cases in which recovery took place.

The advent of modern methods of treatment, including penicillin, offers a better prognosis for a condition which at one time was usually fatal.

## CASE REPORT

*History.* (Adm. #545793) K. M., a white male infant, of 16 days was admitted to the Mount Sinai Hospital on February 26, 1946, for a swelling and discoloration of the right side of the face, accompanied by fever of four days' duration. The infant was born at term in a vertex presentation, delivered by low forceps following a two day difficult labor. No abnormalities were noticed at birth except for a cephalohematoma. He was apparently well until four days prior to admission, when redness and swelling under the right eye were first noticed. At that time his temperature rose to 105°F. on several occasions. The swelling gradually increased in size with the right eye becoming slightly proptosed. Argrol drops were instilled into his right eye without effect.

*Examination.* The infant was well developed and nourished. There was a small right parietal cephalohematoma. The temperature was 104°F., pulse 160. The entire right side of the face was the seat of a marked swelling, which was firm, pitting, red, and had a definite border (fig. 1a). The right eye appeared proptosed and chemotic. The right eyelids were edematous, especially the lower. At the inner canthus of the right lower lid an abscess seemed to be developing. The nostril contained a small amount of non-purulent discharge. In the mouth there were several draining sinuses at the alveolar ridge of the right superior maxilla. A large amount of creamy pus could be expressed from these sinuses. A fine probe introduced into one of these passed directly into an abscess in the bone. The pharynx was normal.

*Laboratory findings.* The white blood count was 28,600 with 70 per cent polymorphonuclear leukocytes. The hemoglobin was 13 Gms. Cultures taken from the nose and throat, from the discharging sinuses, and from the purulent conjunctival secretion, all revealed pure growths of staphylococcus aureus A. The urine was negative. X-ray examination of the face was reported as "a slight density in the region of the maxilla, which could be due to soft tissue swelling. It is impossible to state whether there is any osteomyelitis."

The diagnosis of osteomyelitis of the superior maxilla was nevertheless made and the

<sup>1</sup> From the Pediatric Service of Dr. Murray H. Bass, The Mount Sinai Hospital, New York.



patient was given 10,000 units of penicillin intramuscularly every three hours. In addition 1 cc. of penicillin solution containing 5000 units was injected locally into the abscess cavity on the first day and again on the second. The patient became afebrile on the second day in the hospital. The fistulous openings stopped draining on the sixth day. The swelling, redness and proptosis gradually diminished and had completely disappeared on the fifteenth day (fig. 1b).



FIG. 1a. The patient prior to therapy—the edema and proptosis are evident. b. After therapy—the edema and proptosis have disappeared.

#### COMMENT

Osteomyelitis of the maxilla in infants is generally encountered in their first two months, most frequently in the first two or three weeks of the life of the affected. In most cases, staphylococcus aureus is found to be the infecting agent, although other organisms have been isolated in pure culture. The pathogenesis is not fully established. Some authors believe that a generalized infection pre-exists, and later localizes in the jaw, specifically in the tooth buds. They base this conclusion on the fact that this disease tends to localize where growth is most rapid. The first case of this kind reported in the American literature by Bass (2) in 1928, and the case of Galli's (3), both of which had positive blood cultures, would seem to lend support to this view. Wilensky (1) in agreement with this concept suggests that osteomyelitis of the jaws in infants does not differ from the hematogenous osteomyelitis seen later in life. The preference for localization in the region may be explained by the exposure of this region to trauma, such as occurs secondary to childbirth or, in the postnatal period, to



cleansing of the mouth. An infected thrombus so formed is carried by the blood supply and is then lodged in the rich vascular net surrounding the toothbuds.

There are others who postulate an extension by continuity from a suppurating antrum. Thus this condition was often described as "Empyema of the Antrum" (4), and as "Maxillary Sinusitis of the Newborn." This view does not find support in cases which came to autopsy and which have shown normal sinuses and by cases which have had the osteomyelitic process limited to the inferior maxilla.

Still others believe the primary focus of infection is in the nasal and paranasal structures with the organism being transmitted by way of the lymphatics (5). That in some cases this is the mechanism, was demonstrated by Poncher and Blayney (6). In our case, a primary focus could not be demonstrated.

Although there is no unanimity of opinion concerning the pathogenesis of this condition, all those who have studied it believe that the inflammatory process has its beginning in the anlage of the canines and molars in which the osteomyelitic changes take place. If the infection is not arrested, the process advances into the bone to involve in this way the entire superior maxilla.

The symptoms and signs are predominantly facial, nasal, orbital or intra-oral, depending on which of the surfaces of the maxilla is most affected.

The clinical picture in all cases is quite uniform; the infant, apparently in good health, at the age of 2-10 weeks suddenly develops high fever, becomes anorectic, cries continuously and develops a red, warm swelling on one side of the face, generally in the region of the lower lid. The infant becomes toxic and the swelling generally localizes at the inner canthus of the eye, extending into the orbit, producing a secondary exophthalmos. As a result, marked conjunctivitis develops and soon becomes purulent. This leads one who is not familiar with this condition to the mistaken diagnosis of erysipelas or of purulent conjunctivitis with abscess formation. Sometimes there is also a purulent nasal discharge on the affected side. When the mouth is carefully inspected, edema of the gums over the alveolar ridge and several abscesses are noticed; or if the process is further advanced, several discharging sinuses can be seen. Sometimes at this stage or later, one or more teeth or toothbuds are "discharged." The latter occurrence has been described in about 60 per cent of the cases. If a probe is passed into one of the sinuses, it falls into a large cavity, which is not the antrum of Highmore, but an abscess located in the maxilla itself.

In general, prior to the use of penicillin the disease ran a stormy course. The elevated temperature persisted for many days, during which the infant remained toxic, refused to eat, and cried continuously. Surgical intervention is usually followed by a protracted convalescence. In some cases chronic discharging sinuses yielded unerupted teeth and toothbuds. The formation of Sequestra necessitated readmission to the hospital months later (7 and 8).

Our case, in view of the therapeutic measure, ran a very different course. The temperature became normal 24 hours after treatment was initiated and remained normal thereafter. The sinuses stopped draining on the 6th day, and the swelling of the face soon disappeared. No teeth or sequestra were expelled. This differ-

ence in the course of the present case as compared with those previously reported is undoubtedly due to the use of penicillin. Jacoby and Sagarin (9) in 1945 described three cases treated with penicillin, two of which did not require surgical intervention, and made a good recovery.

It would seem advisable that, once the diagnosis is made, penicillin therapy should be instituted, and it should be administered not only by the systemic route, but also by local injection through the discharging sinus into the alveolar ridge. Sulfadiazine can be added, but is usually unnecessary since in most of these cases *staphylococcus aureus* is the causative agent, which responds to penicillin treatment.

#### SUMMARY

A case of osteomyelitis of the superior maxilla in an infant of two weeks is reported. The etiology of this condition is reviewed and the importance of early penicillin treatment is stressed.

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## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Observations on Mass Chemo-Prophylaxis with Sulfadiazine.* B. W. BILLOW AND M. S. ALBIN. Ann. Int. Med., 24: 863, May, 1946.

Twenty thousand soldiers were given a prophylactic dose of 1 gram of sulfadiazine daily for five weeks. During the prophylaxis period, admissions of common respiratory diseases dropped by 33 per cent. There were no cases of meningitis. Rheumatic fever admissions were cut by 60 per cent. Lobar pneumonias declined by a fourth, while there was a sharp drop (36 per cent) of atypical pneumonias. The drug had no influence upon the incidence of scarlet fever. Sixty-three individuals reacted adversely, none seriously. Thirty of these were hospitalized, some were admitted with a tentative diagnosis of scarlet fever and German measles. It was only after negative throat cultures and observations of the clinical progress, that these diseases were eliminated. Among 33 ambulatory cases, most showed mild skin reaction; a few had angioneurotic edema.

*Coronary Occlusion and Myocardial Infarction.* L. E. FIELD. Correspondence Dep't, J.A.M.A., 131: 354, May, 1946.

The author discusses several criticisms expressed by Dr. Jacobsen concerning publications of Drs. Master, Blumgart, Boas and others. He feels that these criticisms are unwarranted and arise, in part, from a confusion in terminology. The author emphasizes the need for precise use of such terms as "coronary occlusion", "coronary thrombosis", "myocardial infarction", etc., as well as the necessity for employing suitable qualifying adjectives. It is essential to differentiate both clinically and pathologically an acute occlusion from a slow, progressive arteriosclerotic narrowing of a coronary artery. Dr. Jacobsen's comments regarding intra-atheromatous hemorrhage and the role of effort in acute coronary occlusion are analyzed. They are shown to be not substantiated by recent investigations.

*Photography of the External Eye.* H. M. KATZIN. Arch. Ophth., 35: 514, May, 1946.

A camera for photography of the external eye is described, including devices for focusing, illumination and synchronizing the light. The author and his associates have been using this device for three years with good results.

*Progress in Acute Coronary Artery Diseases. Acute Coronary Artery Insufficiency with and without Acute Occlusion.* A. M. MASTER. New York Med., 2: 19, May, 1946.

There are two main divisions of coronary disease, (1) acute coronary insufficiency and (2) acute coronary occlusion. In acute coronary insufficiency there is the simple short episode of angina pectoris, and a severer type in which the anoxia of the heart muscle is more prolonged and serious injury to the heart muscle may take place. The chest pain may be severe and moderately prolonged. The episode is often related to exertion, excitement and emotion. It may occur after sexual intercourse, straining at stool or following a gastro-enteritis. It may be induced by extremes of heat and cold, tachycardia, auricular fibrillation or auricular flutter, shock, heart failure, hypoglycemia, operation, anesthesia, anoxemia of many types, carbon monoxide poisoning, acute hemorrhage, chronic anemia, hyperthyroidism and hypothyroidism. It is a consequence of pulmonary infarction and

embolization, of infection and trauma; it occurs reflexly from abnormal and diseased abdominal viscera. The electrocardiogram discloses depressions of the RS-T segments and T wave inversions in one or more leads. The treatment of the two types of acute coronary insufficiency is distinctive. A rational existence, mentally and physically, will prevent acute coronary insufficiency. During operation or anesthesia an adequate supply of oxygen must be administered, cyanosis must be avoided. Adequate treatment of shock, or better, the prevention of it, are indicated. The administration of digitalis and the mercurial diuretics in heart failure; digitalis and quinidine for tachycardia, auricular fibrillation and flutter; blood transfusions for hemorrhage or anemia; avoidance of reflexes from the abdominal viscera; prevention or cure of infection perhaps with the use of the sulfonamide drugs, penicillin, streptomycin, will all be a means of preventing acute heart muscle damage.

*Bilateral Uveitis with Retinal Detachment, Poliosis, Alopecia and Dysacusia.* J. LAVAL. Am. J. Ophth., 29: 5, May, 1946.

A case is reported of a white female patient who developed the typical changes of edema of the retina followed by detachment, with loss of hair from the scalp, eye brows and lashes with greying of the remaining lashes and with difficulty in hearing. The ocular condition deteriorated so that uveitis with secondary glaucoma developed necessitating operative interference in each eye with resultant vision of 20/100 in the left eye and 20/30 in the right eye. The patient had complete laboratory investigations including spinal fluid cytology and bacteriology. The excised iris tissue was also examined microscopically. No new knowledge as to the etiology of this condition was obtained.

*Occupational Dermatitis.* S. M. PECK. Compensation Med., 1: 13, May, 1946.

Available statistics seem to agree that the annual incidence of occupational dermatoses is at least 1 per cent for all industrial workers. Most of the dermatitis encountered in industry is due to chemicals. Alkalis, petroleum products and solvents are still the chief causes of the industrial dermatoses. Primary irritants are responsible for most of the dermatitis of industrial origin. The sensitizers have received the greatest amount of publicity as causes of industrial dermatitis, in spite of the fact that less than 20 per cent of occupational dermatitis is caused by them. As criteria for diagnosis of an industrial dermatitis, there must be taken into account first—the history, second—the clinical syndrome, third—the site of eruption, fourth—the clinical appearance and fifth—if it is a sensitizer, the patch test. In the discussion of differential diagnosis, a non-industrial dermatitis must be ruled out by a well-trained dermatologist. A special problem is the eruptions which are found on the hands. These must be differentiated from fungus infections found there. In recent years, dermatitis due to plastics has been increasingly important. In this group, the synthetic resins cause the majority of the cases of industrial dermatitis. The synthetic resins which have caused dermatitis most frequently are the phenol-formaldehyde resins, the urea-aldehyde resins, the melamine resins, the sulphonamide formaldehyde resins, the ester gums and the alkyd resins. In this paper also are discussed practical suggestions for dermatitis control and treatment.







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## PROTEIN NEEDS IN SURGERY\*

ROBERT ELMAN, M.D.

Protein, as an important constituent of the body and as an essential ingredient of the normal diet, has only come into its own within the past decade or two. Knowledge of its existence in the diet is scarcely a century old. Apparently the first to realize that the food we eat consists of at least 3 different components, namely fats, carbohydrates and protein, was an American chemist, Prout (15), who in 1836 first pointed out that milk, which he considered to be the prototype of the perfect food, contained each of these 3 substances. He went on to state that each is necessary for food to maintain normal nutrition.

## HISTORICAL SURVEY

The great French physician, Magendie (15), whose fame rested more on his neurological studies than on his interest in nutrition, was apparently the first to distinguish an essential difference between protein, carbohydrate and fat, in that protein contained nitrogen, but not the other two. Nevertheless, it was a Dutch chemist, Mulder (15), who first gave the name protein to the nitrogenous constituent of the diet. He recognized its importance in his choice of the name, which comes from the Greek, meaning primary or first.

During the rest of the 19th and 20th century, one may distinguish 3 distinct periods in the attitude of physicians toward protein: the years up to and including 1900, a midperiod to the end of World War I, and the period since that time.

1. During the early period protein had an important place. The German nutritionists Voit, Rubner and others maintained that a large part of the diet should consist of this food, as much as 100 to 120 Gm. a day for an average sized adult. Throughout the rest of the 19th century this figure was accepted and indicated the importance ascribed to protein in the food intake.

2. During the midperiod beginning with about 1900 protein began to lose its place as an essential and important part of the diet and was relegated to a secondary role. There were 3 reasons for this change. The most important followed the studies and teachings of R. H. Chittenden (3), who for the first time showed that an average sized adult could be maintained in nitrogen equilibrium for long periods with less than half of the protein intake recommended by the older authorities, viz., about 50 to 60 Gm. per day. He went one step further, however, and maintained that this lower intake of protein improved physiological function, whereas any excess was definitely deleterious. This idea, which tended to ascribe some harmful effect to protein, was supported by two other general beliefs, one old and the other relatively new.

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The old belief regarding the harmful effects of protein food stemmed from the early studies on nephritis. Patients suffering from this disease were often found to excrete protein in their urine and many exhibited high levels of nonprotein nitrogen in their blood. From this it was assumed that protein food was deleterious and a low protein diet became routine in the treatment of this disease. For nearly a century this fallacious practice persisted. According to present thought, the loss of protein in the urine calls for an increase rather than a decrease in protein intake in order to correct the deficiency. Moreover, the evils of protein starvation were not recognized until recently. One of the first detailed studies on the beneficial effects of an adequate protein intake in the treatment of children with nephritis (2) appeared less than 20 years ago. Nevertheless, protein restriction is still permitted, even if not actively practiced.

A more recent idea which seemed to support the secondary rôle of protein in nutrition was the conception that the body possessed a large store of protein. This is often referred to as "deposit protein," and presumably is available at all times in order to meet the needs for protein missing from the diet. Indeed, it was stated by no less an authority than Lusk (12) that the "protein reserves of the body are relatively enormous" and that a human being could probably live for over a year without any protein intake whatever.

In view of these general beliefs it is not surprising that most physicians during the early part of the 20th century not only viewed protein restriction with complacency, but even considered it to be beneficial. This attitude held sway until after the first world war. This leads us to the third, or present, period.

3. The third period dates from the observations of two women scientists, Maver (13) and Kohman (11). Working independently, they showed for the first time that "war swelling" or "famine edema," which was very frequent and had been observed for centuries in the wake of war and famine, was actually a clinical manifestation of protein deprivation and not due to toxemia, kidney disease or any of the other causes which have been assigned to this interesting type of symmetrical edema. Several years later these observations were confirmed by Frisch, Mendel and Peters (8). The basic idea, however, had already been investigated by an internist of New York City, A. A. Epstein (7), who maintained that the edema seen in certain patients with nephritis was actually due to protein deficiency. Indeed, he was among the first to recommend the administration of protein in the diet to correct the deficit, thereby going counter to current belief. He was the first to correlate the edema in nephritis with the fall in serum protein, thus applying Starling's hypothesis (17) to a disease condition. Starling in 1895 maintained that the protein content of the plasma exerted a colloidal osmotic pressure which, in balance with the capillary filtration pressure, governed the passage of fluid between the blood stream and the tissue spaces. According to this theory, a deficiency in plasma protein would lower the colloidal osmotic pressure of the plasma, slow the inflow of fluids from the tissue spaces, and thus lead to the accumulation therein of water and salt, producing peripheral edema. Countless observations have confirmed this theory, although there are some who would cast doubt on its validity. Most of



these doubts are a by-product of the fact that there are many other factors which may precipitate or maintain edema entirely apart from the fundamental one based upon the colloidal osmotic pressure of the blood.

During the last decade a great deal of additional information has been obtained about protein in the body and in the food. One of the important observations was made by Weech and his coworkers and others, who, in dogs, showed there was no true source of protein storage material in the body, in that with the very first day of protein deprivation several essential proteins become depleted, notably those in the liver and those in the circulating plasma. Other studies have shown how many clinical manifestations are due to protein deficiency. In addition to nutritional edema they are hepatic insufficiency, a lowered resistance to infection, impaired wound healing, asthenia, decubitus ulcers, and others. Protein has been studied not only for its nutritional significance but also because of its many physical and chemical properties. Much has been learned about the shape, size and behavior of the protein molecule, its variations, and the fact that so many different essential substances in the body, such as hormones and enzymes, are actually protein in nature. The Nobel prize winner, Irving Langmuir, has expressed the belief that many of the primary problems in the conquest of disease are intimately connected with knowledge of the protein molecule and its behavior. An older maxim, attributed to Rubner, "Protein contains the magic of life, ever newly created, ever dying" expressed with prophetic insight the dynamic view of protein metabolism which, half a century later, emerged from the isotope research of Schoenheimer and his coworkers (16).

#### GENERAL CONSIDERATIONS IN THE METABOLISM OF PROTEIN

The metabolic behavior of protein is an interesting and complicated mechanism which cannot even be outlined in this discussion of protein needs in the surgical patient. There are, however, two general considerations which it is necessary to mention, one about which there is general agreement, and the other about which there may be some disagreement.

*Causes of protein deficiency.* There is general agreement about the nature and types of protein deficiencies. Aside from defects in protein synthesis, protein deficiencies result in general whenever the body is in negative balance, that is to say, when the patient has lost more protein than he has received. In such a case the body becomes depleted. A negative protein balance, often spoken of as nitrogen balance, may arise from losses due to one or both of two mechanisms.

1. Actual losses of protein as such, unless replaced, will lead to protein deficiencies. This is common, particularly in surgical patients who have lost blood or plasma, usually following tissue damage or infection. In such conditions the loss involves elements in the circulating blood, i.e., hemoglobin with or without plasma proteins, or plasma proteins with or without hemoglobin. This is true whether the loss is to the outside, as in the case of a cut artery which bleeds from an external wound; into the tissue itself, as in the case of a crushing injury or severe infection; or into a body cavity in the case of peritonitis or empyema. In all of these conditions the loss is an actual one, and unless replaced produces a negative nitrogen balance.

2. In addition to this actual loss of blood proteins as such, all tissue protein (as well as blood protein) is lost through normal metabolic activities. This protein loss can be measured by the nitrogen excreted in the urine and feces, and represents the end product of tissue protein destruction. This includes also losses of blood into tissues or body cavities which are similarly metabolized and broken down to simple nitrogenous substances and excreted in the urine.

Unless replaced by one of the therapeutic procedures to be described later, these losses of protein will be cumulative and lead to a slow or a rapid degree of protein deficiency, depending upon the circumstances in the case. In surgical patients, these losses may be tremendous—as much as one hundred to two hundred grams of protein a day. Translated into muscle tissue, which is 80 per cent water, this would mean the loss of as much as one to two pounds of body weight a day. This is the reason many patients with severe surgical diseases may exhibit such rapid and profound wasting.

3. A third type of protein deficiency will not be considered in this discussion because it involves an entirely different type of mechanism, i.e., a defect in the synthesis of the plasma protein. This exists regardless of the intake of protein, and is seen in at least 2 common diseases. One of them is nephrosis, in which there is a plasma protein deficiency much greater than can be accounted for by the loss of protein in the urine, and which persists even when the individual is maintained in positive nitrogen balance. The other is hepatic disease, in which there is a similar deficiency in the circulating plasma protein due undoubtedly to the inability of the liver to manufacture serum albumin.

*Relation between tissue and blood proteins.* Differences of belief exist in regard to the nature of the relationship between tissue and blood proteins. This disagreement may be expressed by stating the two theories regarding this relationship. According to one theory, the plasma proteins themselves act as the medium of exchange between the tissue proteins and the proteins of the blood. This theory has been advanced by Whipple and his coworkers (19), and is supported by many of the recent studies of the Schoenheimer (16) school, indicating that these plasma proteins may undergo profound changes without being broken down into their constituent amino acids. This theory presupposes, therefore, that plasma proteins, by undergoing certain metabolic changes, may enter and leave tissue cells without losing nitrogen and without the necessity of being reduced to their constituent amino acids.

The second theory is more traditional and is based upon the idea that amino acids themselves or small aggregates thereof are the medium of exchange between tissue and blood proteins, and that the amino acids circulating in the blood stream actually form the basic substance through which all proteins must pass, not only when being assimilated from the gastrointestinal tract from food, but also when one body protein is being transformed into another body protein.

The practical bearing of these two theories concerns the use of whole blood or plasma as a means of introducing protein nourishment through the intravenous channel. If the plasma proteins are indeed the medium of exchange it would

seem logical to use blood or plasma transfusions. On the other hand, if amino acids represent the medium of exchange, it would seem that the intravenous administration of amino acids would be the most appropriate manner by which one could introduce protein through the parenteral channel. In the present author's opinion, the second theory fits most of the facts, first because it is the proved means by which food protein becomes transformed into tissue protein, and second because amino acids circulate in the blood at an even more uniform level than plasma protein. A third reason is based on the fact that each protein has its own individual amino acid composition and it would seem difficult if not impossible to believe that any metabolic process short of an almost complete breakdown to amino acids would permit the transformation of one protein molecule to another.

Finally, recent evidence has cast doubt upon the theory that plasma proteins are actually a medium of exchange between tissue and blood proteins. It was originally believed that because plasma transfusions were followed by immediate positive nitrogen balance the injected protein was utilized by the body, even though most of it had left the circulation. In experiments carried out in my laboratory, however, we found that after cessation of the injection the nitrogen retained during the period of plasma transfusion appeared in the urine in appreciable amounts, so that by the end of the second week much, but still not all, of the nitrogen retained during the period of plasma transfusion appeared in the urine as urea and ammonia (5). These experiments were carried out in dogs. Similar findings have been reported in the human by Meyer et al (14). More complete metabolic studies have been carried out in humans by Fuller Albright (1), who in 2 cases demonstrated a similar phenomenon. He showed that during the period in which the plasma protein is injected, no increase in urinary nitrogen occurs, but that if the patient is studied for a week or two afterwards, an increasing amount of nitrogen is burned and appears in the urine as urea and ammonia. Some is utilized by the body as tissue protein, and a small portion is actually retained in the blood stream. The entire process, however, requires about 6 to 15 days before it is completed.

If we may accept these findings as characteristic of the behavior of a plasma transfusion given to the malnourished patient, we may say that only a portion of the protein so introduced is used in the rebuilding of tissue protein, but that the process is delayed. Thus plasma may, to a certain extent, be used as a source of parenteral protein feeding, even though it does so in a roundabout way, requiring a considerable period. However, these studies offer no support to the idea that plasma protein itself is the medium of exchange. It seems likely that the plasma protein is broken down to amino acids or small peptides by tissue or blood proteases, and thus undergoes the same physiological cycle as food protein before it can be used by the tissues of the body.

These considerations do not mean that transfusions are not valuable in nutritionally depleted patients. They are extremely useful, as will be discussed in detail in the next section, though not as the sole source of parenteral protein food.

## THERAPEUTIC CONSIDERATIONS

In meeting the protein needs of the surgical patient, no attention will be given to those conditions in which there is a faulty synthesis in plasma protein. As mentioned above, this occurs primarily in nephrosis and in hepatic disease, and certainly the latter disease is not infrequently seen by the surgeon. There is a third group, nearly always surgical, in which there is probably also a defect in tissue protein and certainly plasma protein synthesis. These are severely injured or burned patients in whom a severe degree of malnutrition has been allowed to develop. It has long been known that the administration of adequate protein and other food in some of these patients often fails to lead to nutritional restoration. It has been assumed in these cases that there is some defect in the protein synthesizing mechanism, and attempts have been made to correct the fault by the administration of endocrine products, notably testosterone and in some cases the so-called growth hormones, which are known to improve nitrogen retention. In this discussion these fields of therapy will not be included.

The administration of protein in surgical patients will be discussed under 3 subheadings: first, the prevention of protein deficiency; second, the replacement of actual protein losses; and third, the administration of protein food.

*Prevention of protein deficiency.* For the surgeon the prevention of protein deficiency concerns primarily the use of most meticulous surgical technic, whereby the blood loss and the tissue damage are reduced to a minimum. Wound infection must also be prevented, lest loss of protein also occur into the infected area. Open wounds in general lead to a loss of protein, and therefore should be permitted only when absolutely necessary and for as short a time as necessary.

From the nutritional point of view, prophylactic therapy emphasizes the need for maintaining an adequate protein intake from the very beginning of the patient's illness. If the patient comes under our care well nourished, there need be no excuse for permitting more than a very slight protein deficiency to develop, provided the surgeon will meet the patient's nutritional needs from the very beginning. Too often the patient is permitted to develop a protein deficiency while under our very eyes. This may be disastrous, not only because it leads to the clinical manifestations of protein deficiency, but also because it is much more difficult to correct than to prevent a protein deficiency. Thus a correct attitude of the surgeon toward the nutritional intake of the patient from the very beginning of his care will go far to prevent many of the deficiencies which are commonly seen at the present time.

*Replacement of actual protein loss.* The actual loss of protein occurs, as mentioned above, through the escape of whole blood or plasma or both into tissue spaces, body cavities, or to the outside. These losses should be replaced as promptly as possible and nearly always, therefore, require the intravenous route. In many cases, however, the loss should preferably be replaced after the acute phase of tissue injury is over. The reason for this is a likelihood that the early injection of blood or plasma will be only partly effective because most of it will leak out through the damaged capillaries. While an acute urgency exists because of circulatory impairment, such considerations are outweighed by the need



for the correction of shock. Otherwise it is likely that complete replacement of losses from the blood stream is better postponed until the damaged tissue has begun to heal so that the injected blood or plasma will remain in the circulation and not leak out through the traumatized area.

In general, the replacement of protein losses as such with whole blood or plasma transfusion or both is simple and direct, and is deservedly practiced by most surgeons throughout the country. There are, however, certain limitations in the use of whole blood or plasma which will be discussed under the next heading. These limitations refer to their use as parenteral protein food.

The use of whole blood and plasma for the correction of protein losses from the blood stream always involves a discussion of two questions: Which of these two types of transfusions should be used? and how much? They will both be discussed under the heading of whole blood as against plasma transfusion.

*Whole blood*, in contrast to plasma, is used in general when the patient has lost whole blood. Plasma, on the other hand, is used when plasma is the substance which has actually been lost. Knowledge of the patient's disease will usually permit a differentiation between the two requirements. For example, a person who has suffered a severe hemorrhage will require whole blood rather than plasma. A patient who has suffered an extensive loss of plasma through an open granulating wound will obviously need plasma. The conditions in which whole blood is lost are fairly well known. They include actual hemorrhage to the outside as such, bleeding into the tissues, extravasation into body cavities. To this, however, must be added several other conditions in which whole blood is also effective, and these include states in which there has been no actual loss of red blood cells but in which an anemia nevertheless exists. Anemia from any cause is benefited greatly by the injection of whole blood. Such anemias may follow a period of excessive hemolysis; they may occur in patients who have had severe infections in which the production of red blood cells has been impaired. They include malnourished patients or individuals in whom the intake of iron has been restricted.

The use of red cells or whole blood for the replacement of lost hemoglobin is relatively easy and the correction is more or less permanent. This is true because hemoglobin, unlike the albumin and globulin of plasma, is an intracellular protein and thus does not leave the circulation after injection, even when the patient has become anemic because of malnutrition.

In addition to these conditions of blood loss certain types of injuries seem to be benefited by whole blood even though there is no actual anemia. For example, certain types of burns in which toxic signs develop during the acute stage seem to benefit more by whole blood than by plasma transfusions. Other cases, some with infection, seem also to benefit from injection of red cells, which exert an effect entirely apart from their content of hemoglobin. The reason is not clear.

The amount of whole blood required is relatively easy to determine, based upon successive red blood counts, by hematocrit determinations or hemoglobin measurement before and after the transfusion. In general, one liter of blood



will raise the red count about 500,000. The best procedure is to add a sufficient amount of blood to the circulation until the count returns to normal. On the other hand, the presence of a normal red count should not deter a surgeon from administering whole blood if the history suggests that it is required. The reason a normal red count may be found in a patient who actually needs whole blood is the contraction of the total circulating blood volume which thus masks the deficiency.

*Plasma* transfusions are, in general, indicated when there is an increase rather than a decrease in the red blood cell count. These commonly occur in any condition in which the plasma portion of the blood has been lost such as in intestinal obstruction, severe peritonitis, pneumonia, extensive extravasating wounds and similar conditions. Plasma transfusions for the correction of hypoproteinemia of nutritional origin is another matter entirely, and is usually disappointing, for reasons to be discussed below.

In most cases, at least 500 cc. of plasma will usually be necessary and more may have to be given if the condition for which it has to be used has not satisfactorily improved. In a severe burn, for example, as much as a liter or two of plasma may be required to correct the hemoconcentration and the circulatory impairment which sometimes goes along with it. In many cases both whole blood and plasma may be required in the same patient, although usually at different periods in the treatment. For example, a burn may require a liter or two of plasma on admission for rapid correction of severe shock and hemoconcentration. After a few days the blood count may fall below normal, thereby calling for the use of whole blood to correct the anemia.

In general, the decision as to the use of whole blood or plasma must be based upon the considerations in the individual case. There seems no justification for the use of either one or the other exclusively in the treatment of surgical patients.

The above-mentioned considerations apply when both whole blood and plasma are available. It is obvious that in the absence of whole blood, plasma is probably by far the best blood substitute. As such it undoubtedly saved a good many lives during World War II whenever whole blood was unavailable, even in patients who had lost a good deal of blood by hemorrhage. On the other hand, in the absence of plasma, whole blood is much more effective than any other substance, even when the red blood count is high. Insufficient study has been made, however, to indicate the degree of difficulty imposed upon the body when an excessive amount of red blood cells are presented to the circulation. Indeed, the author once saw a patient who was given so much blood for the treatment of a nutritional anemia that the circulation became overloaded and it was necessary to bleed her in order to correct the hemoconcentration.

*Protein food.* Under normal circumstances, the protein in the food we eat is the source from which body proteins are maintained, and losses sustained in normal physiological activity replaced. Even under most conditions of disease, losses of protein are met satisfactorily by the ingestion of an adequate amount of protein in the food. The only reason acute losses, as already described, should be met by the injection of whole blood or plasma is the fact that replacement

will lead to more rapid clinical improvement. The only other indication for the use of the parenteral channel is the inability of the patient to eat. This will be discussed separately.

Although it is obvious that protein food by mouth is essential in order to maintain body protein and to replace losses therefrom, it is remarkable how prevalent are protein deficiencies in most hospital patients. Many patients quite able to ingest sufficient protein to maintain their body tissues and thus prevent protein deficiencies are actually allowed to suffer protein deprivation. The physician must realize this danger and adjust his treatment of the patient with an adequate intake of protein from the very first. To be sure, many patients are already malnourished when we see them, and this increases the problem immeasurably. Only when the general public has been taught that protein deprivation is harmful and to seek prompt medical advice when eating is impaired will this situation be greatly alleviated. But when the patient is already well nourished there is no excuse for the development of protein deficiency at the present time. Even if the patient cannot take anything by mouth, protein foods can now be given parenterally.

A common mistake in the administration of protein food by mouth is the assumption that the ordering of an adequate diet is equivalent to the consumption thereof. Scrutiny on the part of the physician will frequently reveal that only a very small part or none at all of the excellent diet he has ordered is actually consumed. Only by direct interest in the problem of the consumption of food by his patient will the physician realize this disparity.

In the patient who is able to eat the usual amount of food, a show of interest by the physician in charge will often be enough to assure its ingestion. A word from the doctor will often make all the difference in the world between the patient's consumption of the diet and his leaving the tray only partially consumed. When such a simple method works, the problem is readily solved.

Many patients, unfortunately, are unable to consume a normal diet. They may be too ill to masticate solid food, or they may be unable to retain all the bulk which comprises a normal diet. In these patients it is necessary to use certain special devices in order to prevent protein deficiencies. Two factors are mainly concerned in such devices. One is the use of some liquid diet or soft diet which will spare the need for mastication, which is an important feature in many sick patients. The second factor is the reduction of the bulk of the diet, which can readily be achieved in many cases by reducing the amount of carbohydrate and fat which it contains. This is justified because adipose tissue, the only body food which is really dispensable, can be readily used to furnish calories when an insufficient number is present in the diet. It has been shown, however, that at least 100 Gm. of carbohydrate must be ingested by the patient in order to prevent ketosis, and to avoid unnecessary breakdown of body tissues. This amount is therefore the minimum of carbohydrate required. To this a sufficient amount of protein should be added, usually 100 Gm. Thus, for an adult patient unable to eat a normal diet, 100 Gm. each of protein and carbohydrate would represent the minimum intake in order to prevent protein deficiency. Such a minimum

intake may be made into a liquid, high-protein drink with great ease, and may be ordered as medication, which assures its ingestion by the patient. With this intake it is unlikely that many patients will develop protein deficiencies, and indeed, many of them may actually correct protein deficiencies to a slight extent. For seriously depleted patients much larger intakes will be needed if restoration is to be promptly effected. Actual experience has shown that with special care as much as 250 Gm. of protein and 5000 calories can be given by mouth (19).

Perhaps the simplest way in which a high protein liquid diet can be made is to use skimmed milk powder, which contains by weight about 35 per cent protein and about 50 per cent carbohydrate. Thus, 300 Gm. of skimmed milk powder a day will give the patient a minimum of 100 Gm. of good quality protein per day. This powder may be made into a drink or it may be added to soups, cereals or other foods which the patient is able to ingest. Skimmed milk powder is relatively inexpensive and need add very little to the patient's hospital cost. Many proprietary mixtures of skimmed milk powder or other proteins have been placed on the market and may be employed for convenience. Other types of soft or liquid high protein drinks or food may be devised by any ingenious dietitian. Meats are now available in semi-solid or almost liquid form. These special devices, however, are only used temporarily until the patient is over his disability or disease. As soon as possible normal foods, including the high protein ones such as eggs, meat, fish and milk, are added.

*Hydrolyzed protein by mouth.* There may be certain surgical patients who may with profit be given hydrolyzed protein by mouth rather than normal whole protein. It is difficult to state exactly what the indications for such predigested protein may be. In general terms it would include patients in whom we wish to spare the need for digesting protein. It would include patients whose gastrointestinal function is impaired and in whom the ingestion of whole protein results in disturbances such as diarrhea. In other cases the ingestion of hydrolyzed protein will permit the administration of much larger amounts of protein, since the need for digestion is obviated. This would apply to patients who are greatly depleted and in whom a correction of the protein deficiency could obviously be reached within a shorter period of time, with a larger daily intake of protein. In ulcer patients with hyperacidity the ingestion of hydrolyzed protein may be indicated because it is a better buffer than whole protein.

Hydrolyzed protein preparations at the present time are unpleasant to drink because of their bad taste. This is a handicap which will be aggravated if the physician or surgeon sympathizes with the patient. When ordered without question as a necessary part of the treatment, many patients object much less to the taste for the short period in which this method of administration is necessary.

*Parenteral protein feeding.* There are two ways in which protein may be given through the parenteral channel. One is by means of whole blood or plasma transfusions, and another by the injection of appropriate amino acid mixtures which at the present time are available commercially only as solutions of hydrolyzed protein. The use of whole blood and plasma transfusions for the replacement

of losses from the blood stream has been discussed already. The use of whole blood and plasma as a source of protein food presents an entirely different situation. It presupposes that the whole protein molecule thus introduced into the blood stream can be utilized effectively as a source of nourishment for the rest of the body. The evidence for and against this theory has already been discussed. From the evidence now available it would seem that this method of protein feeding is not immediately effective and is probably not as efficient as a more physiological approach, for which amino acid mixtures themselves are injected directly into the blood stream. This will be discussed in detail below.

The use of whole blood or plasma transfusion in protein-depleted patients should be immediately effective if it served the purpose of replenishing the deficiency in the blood stream itself. This it does as far as the hemoglobin is concerned, as already mentioned, so that the use of whole blood as a source of protein food to meet a deficiency in hemoglobin is most satisfactory. The same, unfortunately, is not true of plasma proteins, inasmuch as the plasma which enters the blood stream either as a whole blood or plasma transfusion, not being intracellular like hemoglobin, rapidly leaves the circulation and enters the protein metabolic pool, as already discussed. This explains why it is so difficult, if not impossible, to correct a nutritional hypoproteinemia with whole blood or plasma transfusions unless given repeatedly and in large amounts. Entirely apart from its ineffectiveness in this regard are the disadvantages of administering large amounts of whole blood or plasma as the sole source of protein food. Each liter of plasma contains about 6 Gm. of sodium chloride and about 10 Gm. of sodium citrate, which is really not needed by these depleted patients. Worse than this, the administration of salt intravenously in malnourished individuals has long been known to be particularly harmful, and may, in some cases at least, lead to so-called salt edema.

Other differences between injections of plasma protein and hydrolyzed protein may be mentioned. The incidence of reactions seems somewhat similar, except for homologous serum jaundice, a danger which is true only of plasma transfusions. The cost of plasma is important, when purchased commercially: \$1.75 per gram as compared with 4 cents per gram for hydrolyzed protein. One liter of plasma, yielding about 60 Gm. of protein, requires the bleeding of 4 donors.

If one must use the parenteral channel, it would seem, *a priori*, that the use of an appropriate mixture of amino acids would be the most physiological method, inasmuch as this is the normal way in which protein is assimilated by the body. The only difference between the parenteral and the normal method is the fact that the injected amino acids enter the systemic circulation rather than the portal system, which is the case when protein is taken by mouth. Sufficient study, however, has shown that the actual difference between the entrance of amino acid in the two systems is not marked. For many years now amino acid mixtures have been injected parenterally both to animals and to patients, and the evidence of its value as a source of protein food may be briefly summarized. One of the ways in which the efficacy of protein food may be demonstrated is its ability to maintain nitrogen balance when fed as the sole source of nitrogenous



nourishment. Thus, if a mixture of amino acids is given parenterally as the sole source of nitrogen and leads to nitrogen balance, i.e., provokes a loss of nitrogen equal to or less than it contains, one assumes that the material is used, in part at least, for the synthesis of body tissue protein. In a typical case a patient, unable to take food by mouth, is given the ordinary injection of water and saline. Under these conditions he will lose from 5 to 20 Gm. of nitrogen a day in his urine. This represents a loss of 30 to 125 Gm. of dry protein tissue, or, translated in terms of muscle, the breakdown of 150 to 600 Gm. of tissue. If one now adds to this glucose mixture a sufficient amount of an amino acid mixture which will balance the nitrogen loss, or which contains more nitrogen than is excreted, one may say in the first case that the loss of protein tissue has been replaced and that in the second case, additional protein tissue has been fabricated from the amino acids which have been introduced. Though some question has been raised as to the validity of nitrogen balance studies as a measure of tissue protein synthesis, most authorities would accept this device as a method of measuring the efficacy of any protein, whether given by mouth as such, or by the parenteral route as an amino acid mixture.

In the case of surgical patients before operation, positive nitrogen balance has been achieved repeatedly with the use of parenteral solutions of hydrolyzed protein as the sole source of nitrogenous nourishment. After operation, at least with moderate amounts of amino acids, it is much more difficult to demonstrate a positive nitrogen balance, but in any case it is always possible to lessen to a considerable extent the large loss of nitrogen which is so commonly seen after trauma. For example, the average daily loss of nitrogen after operation may be between 10 and 20 Gm. If 12 Gm. of nitrogen in the form of a hydrolyzed protein solution is added to the parenteral fluid, the nitrogen excreted will increase, but the negative balance is reduced, on the average, to about 3 Gm. of nitrogen, thus preventing the wastage of about 8 to 15 Gm. of nitrogen, or, in terms of tissue, 250 to 450 Gm. per day.

A second method by which the nutritional value of protein food can be demonstrated is the measurement of its effect on regeneration of plasma protein. Animals are first depleted by a protein-free diet. When given an adequate solution of amino acids or of hydrolyzed protein, they will fabricate serum albumin almost as well as when fed protein by mouth. In humans a similar demonstration has also been made, although the evidence is not quite as extensive. The reason is that one is not justified in using the parenteral channel for long periods of time in the human, since in most clinical cases the patient is put on an oral intake as soon as possible. Inasmuch as it usually takes a long period to demonstrate increases in serum protein, which form but a small fraction of the total protein in the body, such long term observations in the human have seldom been carried out.

A third and perhaps a better method than the measurement of serum protein regeneration would be the direct demonstration of tissue protein synthesis itself. This could be readily done with the liver as the tissue studied. Such experiments are now under way.



There are two other ways in which the efficacy of protein food has been determined, at least as applied to the oral route. One of them concerns the ability of the material to promote a normal growth in immature rats given the protein preparation as the sole form of nitrogenous nourishment. Indeed, this test is a most rigid one in determining the presence of the essential amino acids in adequate amounts. The other method is the ability of the preparation, when given as the sole source of nitrogenous nutriment, to promote normal weight gain in adult animals who have been depleted by the ingestion of a protein deficient diet. Neither of these methods has been extensively used for testing hydrolyzed protein used parenterally.

A sixth method might also be mentioned, and that is the analysis of the protein for its content of essential amino acids. If sufficient amounts are present, it is assumed that the preparation is adequate.

Entirely apart from these metabolic and biochemical considerations, considerable clinical evidence is available that the use of parenteral protein feeding is of benefit to surgical patients. Such observations, being subjective, will obviously have much less scientific value. Nevertheless, many patients have been treated with and without this addition to the parenteral regimen, and several differences noted. For over a decade or more practically every patient unable to take anything by mouth was given a solution containing glucose, vitamins, and a certain amount of salt. The behavior of such patients is relatively easy to compare with those in whom an amino acid mixture has been added.

These observations may be briefly summarized. The preoperative use of amino acid mixtures in addition to the usual glucose injection has resulted in a much better condition of the gastrointestinal tract, particularly in patients with various types of obstruction and with fistulas. To be sure, other methods of preparation also contribute to this desirable state. The evacuation of obstructed gastric contents and the decompression of distended intestine is of primary importance. The use of parenteral feeding, however, so improves the condition of the tissues in the gastrointestinal tract that edema is less evident or completely absent, the empty, collapsed stomach and intestines are much easier to handle and to dissect, anastomoses are much simpler and healing much more efficacious. Moreover, patients are able to withstand much more extensive surgical procedures when prepared this way than when given only glucose and water as the sole nutritional intake.

After operation, patients in whom protein starvation has been prevented by the administration of amino acids seem to be stronger, are more likely to start early movement, and are far more likely to ask for food earlier than patients given glucose alone. It is therefore possible to shorten the period of postoperative disability, and indeed to start patients on a normal oral intake much sooner than was the case when glucose alone was given. In addition, we have seen much fewer postoperative difficulties due to obstruction at anastomoses, particularly after gastroenterostomy. Wound infections seem to be much less prevalent, although this has not been a great problem in recent years. Wound healing

is also improved, although here again, with the use of non-absorbable sutures and with adequate preoperative preparation, the use of vitamins and the avoidance of too much fluid, particularly saline, after operation, these complications have not been very prevalent in recent years.

The ability of the parenteral injection of amino acids to control the feeling of hunger has been subjected to some inquiry. We have made a number of observations which suggest that glucose alone in patients with duodenal ulcer will not control pain, whereas the addition of amino acids has actually done so. In many patients the injection of amino acids has provoked the voluntary statement that their hunger has been controlled. For a long time there seemed no physiological basis for this effect, but within the past year observations have been made in this clinic by Crider and Walker (4) on a patient with a large fistula of her stomach, indicating that the intravenous injection of amino acids decreases the resting activity of the stomach, whereas no effect was produced by a similar injection of glucose alone. These observations suggest that the entrance of amino acids into the blood puts the stomach completely at rest. If hunger is actually due to gastric activity, this furnishes a basis for the bedside observation that hunger may be controlled in this way.

To mention a specific type of surgical disease which has been especially benefited by the parenteral use of amino acids, I would cite my experience with about 12 patients with multiple intestinal fistulae due either to difficulty following the drainage of an appendiceal abscess, operations for intestinal obstruction, the presence of regional ileitis, or an obstruction following an enterostomy. By adequate preparation before operation it was possible to improve the local lesion as well as the general nutrition so much that the patients were in a condition which permitted a safe one-stage resection of the fistulas and the damaged bowel, and to perform an anastomosis with complete closure of the abdomen. Most of these patients were extremely malnourished, and therefore were in poor condition to withstand surgical procedures of any extent. Yet oral feeding usually aggravated their local and general condition. In each of these cases the entire surgical procedure was carried out without mortality.

In the practical care of the extremely depleted patient unable to eat, both blood and amino acids are used for the parenteral administration of protein. Each has its place and serves a somewhat different purpose. For the immediate nutrition of tissues, amino acids should be introduced in amounts of 100 Gm. or more a day plus the same amount of glucose, some salt and vitamins. Generally, only 2 liters of water need be given for maintenance in the absence of pathological fluid losses. Whole blood should be given in addition, largely to restore the red cell mass to normal. Plasma transfusions will also be of value because they will to some extent increase the level of plasma protein. The salt content of plasma is a real disadvantage, but has been eliminated by the newer preparation of salt-poor human albumin, which has been shown to be much more valuable. Unfortunately, this material is not yet available commercially except at a cost which is beyond the reach of most patients.

Protein needs have important relationships with each of the other elements in the diet. Only one, glucose, will be discussed, largely because of its practical bearing in the patient who must be fed parenterally. One might assume, *a priori*, that all of the caloric needs should be met and this is, of course, possible, but difficult. To supply 1600 calories, 4 liters of 10 per cent glucose or 8 liters of 5 per cent glucose would have to be injected, an obviously inconvenient and expensive task. Inasmuch as adipose tissue is a true body store it can presumably supply much of the energy needs without physiologic impairment. As already discussed under oral protein feeding, this reasoning justifies considerable reduction in the caloric intake. From a variety of observations it has been shown that 100 Gm. of glucose for the average sized adult is probably the minimum requirement. Gamble and his coworkers (9) have shown that 50 Gm. is not enough, but that there is no improvement in nitrogen-sparing if the amount is increased to 200 Gm. This is in accord with our own observations. Thus it would seem that a daily intake of 100 Gm. of glucose is adequate, for a limited period at least, and thus meets minimum needs.

#### SUMMARY

In the century since protein has been known as a constituent of the body and of the diet, its importance seems now established. The harmful effect of deficiencies in protein are now generally recognized. The need for preventing or correcting them is being more widely met. To do so is not always simple and often requires some knowledge of essentials of protein metabolism on the part of the surgeon.

Protein deficiencies result because of faulty synthesis or unreplaced losses, the latter comprising both actual and metabolic losses. The treatment of faulty protein synthesis continues to be unsatisfactory because the causes are still unknown. Protein deficiencies due to losses can be nearly always prevented and frequently corrected if all available methods are properly used. These include, (1) the adequate administration of protein by mouth, (2) the injection of whole blood and plasma, or their derivatives, (3) the ingestion or injection of appropriate amino acid mixtures.

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# A DISCUSSION OF THE LESIONS OF THE PANCREAS AMENABLE TO SURGERY\*

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During the past ten years, interesting changes have taken place in the philosophy of American surgery in different categories of lesions requiring operative procedures. In the acute inflammatory lesions, chemotherapy has had a definite effect on the type and extent of surgery. In a number of the chronic inflammatory lesions less radical resection and more efforts to restore function are followed. On the other hand, in the field of malignant neoplasm, surgery has become much more radical with a better understanding of maintaining fluid, electrolyte, protein and hemoglobin balance, nutritional needs, and prevention of infection and postoperative complications.

Certainly these changes are evident in the surgical therapy of pancreatic lesions. I can well remember years ago when acute pancreatitis, then recognized only in its most severe forms, was considered an acute emergency. Patients were rushed from the admitting ward to the operating room, in shock, with hemoconcentration and vasomotor collapse. Attempts were made by some surgeons to incise the capsule of the enlarged pancreas and to poke holes in the seriously damaged organ. The operative mortality was dreadfully high, well over fifty per cent. The only other lesions of the pancreas considered amenable to surgery were the cysts which were marsupialized to the abdominal wall,—followed often by persistent pancreatic fistulae. Tumors of the organ were considered untouchable except for a rare benign type of neoplasm.

Today the attitude has changed remarkably. Because of the serum amylase test, acute pancreatitis is diagnosed much more often but operated upon far less frequently than formerly. On the other hand, for neoplasms of the organ, partial and even total pancreatectomy is now being done in many of our surgical clinics in increasing numbers. The pancreas is no longer a *noli me tangere*, but is approached far more rationally than ever before.

The lesions which now are amenable to surgical therapy may be grouped as follows: 1. In subsiding acute inflammation with abscess formation; 2. In chronic inflammatory lesions with fibrosis of the organ and calcareous deposits in the duct system or more rarely in the parenchyma of the organ; 3. For drainage of pancreatic cysts, rarely for excision of the cyst; 4. For tumors, benign and malignant.

*Acute pancreatitis.* The use of the serum amylase test in the differential diagnosis of acute upper abdominal lesions has emphasized the fact that the less acute forms of pancreatitis such as edematous and non-gangrenous inflammation are

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much more common than was formerly known. Acute pancreatitis, as now recognized, may vary from an acute edema to a necrosis of part or all of the organ. The pathogenesis of these several varieties of acute inflammation is still a controversial subject. But in general it may be said that two factors are always present: (1) an inciting agent, chemical or bacterial, entering the pancreas by way of the blood, lymphatics or ducts, which activates the proenzyme trypsinogen, converting it into trypsin; (2) obstruction of the duct system. The degree of the activity of trypsin in causing an edema or an auto-digestion of the blood vessels and parenchyma of the organ and the amount of obstruction of the duct system, determines the type and severity of the inflammatory process.

With any degree of duct obstruction as a result of early edema there is a variable block in the outflow of the pancreatic juice with absorption into the blood of the enzymes. This can be most easily determined by testing the blood serum for amylase.

In the clinical picture of these severe lesions, shock is the most serious phase of the symptoms and signs. In the milder form of edema of the pancreas, shock is usually not evident, but in the hemorrhagic and necrotic varieties, shock is so serious that it is the only condition that should be treated at first. It is manifested by great hemo-concentration, low blood pressure, rapid pulse and vasomotor atony. It should be treated by plasma transfusion, physiologic saline solution and adrenocortical extract. If surgery is resorted to before the shock is relieved, the mortality will be as high as it has always been—around 50 per cent.

Inasmuch as the same symptom picture is seen in other acute upper abdominal lesions, especially in high-strangulation ileus and perforated ulcer, in which operative delay is so hazardous, the differential diagnosis of acute pancreatitis is most essential. It is in these conditions that serum amylase and lipase readings are of the greatest help, as are three-position films of the abdomen to determine fluid levels in the small intestine in ileus and in subphrenic and subhepatic air in perforation of the gastrointestinal tract. If serum amylase readings are definitely elevated and fluid levels and free air are ruled out by x-ray examination, the diagnosis of acute pancreatitis can safely be made, the patient can be treated for shock, and surgery can be delayed. Many of these patients, the majority in fact, show such marked improvement in six to twelve hours that surgery can be postponed for associated biliary lesions or for localizing pancreatic inflammation or abscess formation. There is no doubt that this conservative policy, now followed in a number of surgical clinics in various parts of the country, has lowered the mortality of acute pancreatitis. In our experience in the past five years, the mortality has been 15 per cent in 46 cases of acute pancreatitis of various grades, as proved by delayed operation or by autopsy. In the two previous five-year periods, when operation was done as soon as the diagnosis was made, the mortality had been 34 per cent.

*Chronic pancreatitis.* Chronic pancreatitis, even with marked fibrosis and calcareous deposits and diminished external secretion, gives a variable symptomatology and clinical picture. Diabetes or jaundice may or may not be present. Digestive disturbances, especially in the ability to digest fats or fatty derivatives,

are usually present. But it is the presence of severe intolerable pain, especially in the lesions showing calcareous deposits in part or all of the organ, and not responding to any form of conservative therapy except morphine, that brings the patient to the surgeon. This pain is usually a deep, boring epigastric pain radiating to the back. Duodenal studies with mechohyl injection to determine the presence, diminution, or absence of pancreatic ferments or of blood, urinalysis, and blood sugar determinations, and x-ray films of the upper abdomen to demonstrate pancreatic calculi or calcareous deposits are the essential laboratory studies. The presence of jaundice and absence of crystals together with the presence of blood in the duodenal contents, points more definitely to a neoplasm of the pancreas, especially if the patient has lost weight and has a distaste for food. In our experience all the cases with calcareous deposits have been associated with chronic fibrous pancreatitis rather than with cancer.

At this point it is pertinent to discuss the differential diagnosis of obstructive lesions in the ampullary area, due to common duct stone, common duct neoplasm, chronic pancreatitis, carcinoma of the papilla of Vater, and carcinoma of the head of the pancreas. Ågren and Lagerlöf (1) of Stockholm deserve real credit for developing the double tube duodenal intubation for the study of the duodenal bile and pancreatic ferments. Using secretin intravenously, which was crystallized by Hammersten, as a hormone stimulator of the pancreatic ferments, they determined the quantitative function of the pancreas. Mecholy, acting on the vagus mechanism, can be used instead, giving a qualitative determination. Studying the bile, recovered by this intubation, for crystals and detritus, and determining the presence of blood, give the three differential factors. Thus in a carcinoma of the papilla there is an absence or great diminution in the pancreatic ferments, an absence of bile, and the presence of red blood cells. If the obstruction is due to a carcinoma of the common duct above the papilla, pancreatic ferments will be present, diminished or absent bile, no crystals, and red blood cells may be abundant. A carcinoma of the head of the pancreas may show little if any enzymes, abundant crystal-free bile, and red blood cells. Common duct stone will usually show pancreatic ferments, no blood, and diminished bile containing cholesterol crystals or bile pigment concretions.

Well over 1000 such tests with mecholy have been carried out at the Presbyterian Hospital. Both Dr. Bauman and I consider duodenal intubation an important aid in the differential diagnosis of these lesions.

The only indications for surgery in these patients is intractable pain which is associated with or threatening morphinism. A sufficient number of such patients have been operated upon, with radical removal of part or all of the pancreas, at the Presbyterian Hospital, New York City, and at the Mayo Clinic, with complete relief of their pain to prove the efficacy of the operation. But some two years ago Dr. Reginald Smithwick (2) of Boston demonstrated the same relief of pain in such a case with multiple calcareous deposits by a thoracolumbar sympathectomy. Since then he and Dr. Bronson Ray of the New York Hospital have successfully carried out this procedure in a number of patients.

This procedure is far less hazardous immediately than a partial or complete

pancreatectomy, in the latter with a diabetic future. However, the removal of pain compromises the recognition of a subsequent acute inflammatory lesion such as I have recently observed in a patient who had had a thoracolumbar sympathectomy. She had no pain or tenderness, but she had an epigastric palpable mass, a leucocytosis, and a continuous fever, as well as a displacement of her stomach and duodenum, demonstrated by a barium x-ray study. But the relief from pain and morphinism in this group of patients, whatever the operative procedure, is a blessed relief to an otherwise intolerable existence.

*Pancreatic cysts.* The differential diagnosis of pancreatic cysts will always be a fascinating problem in abdominal masses. A recent history of upper abdominal crisis or trauma should always make one think of pancreatic pseudocyst in the presence of a mass in the upper abdomen, especially one to the left of the midline. These so-called "pseudo-cysts" following trauma or acute pancreatitis develop, as a rule, more rapidly than the retention cysts, the cystadenomatous cysts and the so-called "dermoid cysts" in the pancreatic area. The pseudocysts are unilocular, are usually not lined by epithelium, and when marsupialized or drained are not followed by persistent fistula, as a rule, and therefore give better late results. In the diagnosis of any large pancreatic cyst, a simultaneous barium meal and a barium enema for x-ray studies are of great help in differentiating the lesion from splenomegaly, renal tumor, mesenteric cyst and retroperitoneal masses. A pancreatic cyst pointing forward through the gastrohepatic omentum will push the stomach downward; one pointing through the gastrocolic omentum will push the stomach upward and the colon downward; and one pointing through the mesocolon pushes the colon upward.

Only a small percentage of pancreatic cysts can be completely removed, because of their deep position, their relation to vital structures, and their frequent association with large, friable, vascular channels. For this reason, when one explores the abdomen and finds such a cyst, it is imperative to determine by careful inspection, before any attempt is made to excise it, the question of whether or not the cyst is removable, for once the attempt is begun, if it has to be abandoned because of hemorrhage or damage to such vessels as the midcolic, the superior or inferior mesenteric, or the portal vein, the mortality rate rises to a high level.

Formerly in cysts that could not be removed, the accepted procedure was to marsupialize or suture the cyst wall to the skin of the abdominal wall and then to drain it externally. This is usually satisfactory for the pseudocysts, but a pancreatic fistula may persist, and usually does if the cyst wall is epithelialized with secretion of pancreatic juice or mucus.

More recently the procedure of uniting an opening in the dependent portion of the cyst wall to the stomach or to the upper jejunum, to form an internal fistula, has been used by a number of surgeons and in my own experience the results have been very satisfactory.

*Tumors of the pancreas.* A discussion of the surgery of the tumors of the pancreas is a complex subject, surgically simple and agreed to when the growths are benign, but complicated and controversial when they are malignant. Before the discovery of insulin in 1922, which clarified the question of the internal secre-

tion of the pancreas, only a small number of successful removals of benign tumors had been reported. In 1924, Gross and Guleke (3), in their comprehensive monograph on the diseases of the pancreas, in the section on the treatment of tumors of the pancreas, were able to find only six cases of benign tumors removed by operation and reported in the literature. With the report by Wilder and his associates (4) in 1927 of the carcinoma of islet tissue operated on by Dr. Mayo and the paper of Howland et al describing the first successful removal of an islet-cell adenoma by Dr. Graham (5) in 1929, a new field of endocrine surgery was opened, and since then, in a period of twelve years, over 200 islet-cell tumors have been reported. Probably as many more have been removed but not reported. The pathology, the typical syndrome, the diagnosis, the indications for surgery, and the technique of the operation in this group of lesions have now become clarified and standardized, and the results, in qualified hands, are amazingly good.

*Islet-cell tumors.* The majority of islet-cell tumors are microscopically benign adenomas, but a certain number are questionably malignant because of capsule invasion or the finding of islet-cells in the blood vessels of the tumors. A minority of such tumors are obviously malignant, as shown by metastases to the liver or adjacent lymph nodes.

It is impossible in this lecture to go into the details of the pathology, symptomatology and treatment of these tumors, but certain points should be emphasized.

Disorders of the liver, adrenal, pituitary and thyroid glands, and thalamus, in which hypoglycemia occurs, must be ruled out.

The syndrome (6) associated with islet-cell tumors must present the following essential triad: attacks of central nervous system disorder—motor, vasomotor or psychic—in a definite individual pattern, coming on during the fasting state; fasting blood sugar levels of 50 mg. per 100 cc. or less; and immediate recovery from these attacks on the administration of glucose by mouth or by vein. Unless this triad is present, the diagnosis of a tumor requiring surgery should not be made. In a review of 105 cases of islet-cell tumor removed by operation, only one patient showed a fasting blood sugar above 50 mg. per 100 cc., and his reading was 53 mg. Because we have adhered to this rule, we have found islet-cell tumors at operation in 35 of 41 patients, whereas in another clinic, in which the rigid criteria were not followed, tumors were found in only 16 out of 46 cases.

In the majority of epileptic and narcoleptic patients with disturbed blood sugar levels, the triad is not found, but in the doubtful cases, electroencephalograms now give tracings characteristic of epilepsy and help to establish the differential diagnosis.

In patients with the definite triad in whom serious hepatic, pituitary, adrenal and thyroid disease has been ruled out, surgery is definitely indicated and should not be delayed, for the following reasons: the continued enormous daily intake of carbohydrate required to prevent hyperinsulin shock results in rapid and marked obesity and makes these patients bad operative risks, and the surgical procedures exceedingly difficult; the repeated attacks of insulin shock or pro-



longed hypoglycemic states favor subsequent mental instability and deterioration, and the tumors, if questionably malignant while still localized, may metastasize and become inoperable.

In an exploration for these tumors, a thorough search of the mobilized tail, body and head of the pancreas by inspection and palpation must be made, to reveal the tumor or tumors, for more than one may be present. To palpate the head of the pancreas the duodenum must be mobilized to the left, exposing the posterior surface of the head. We have found more than one tumor in four cases, and we have removed a tumor from the posterior aspect of the head in six patients who had previously been unsuccessfully explored. Six other such secondary operations have been reported, and in three autopsies, tumors overlooked at operation have been found.

After such a thorough search has been made and no tumor found, the question of subtotal pancreatectomy must be decided.

It is evident that the patients with excised tumors give far better results than the partially pancreatectomized cases and that the patients in whom no tumor is found give about 60 per cent cures if 40 to 60 gm. of pancreatic tissue is removed (7).

In the study of these islet-cell tumors, certain incongruities are notable. The size of the tumor has no relation to the severity of symptoms. The largest tumor in our series gave no symptoms of hyperinsulinism and did not suggest the islet tumor syndrome. Brunschwig's (8) patient, who had the largest tumor on record (15 x 13 x 10 cm.), did not have lower fasting blood sugar values or more severe symptoms than many of those with tumors 1 or 2 cm. in diameter. A patient may have a severe convulsion one day, with a fasting blood sugar level of 45 mg. per 100 cc., and only slight confusion or disorientation the next day, with a reading of 30 or 25 mg. per 100 cc.

The blood sugar level after a fast of fifteen to twenty hours, or until the patient's pattern of attack appears, is a far more reliable test of islet-cell function than the glucose-tolerance curve. We have come to consider the latter entirely unreliable as a differential test, and regard it as a liver-function rather than a pancreatic-function test.

The role of the other organs of internal secretion in the hypoglycemic state of islet-cell tumors is not understood and offers room for much speculation. Without doubt, the pituitary, adrenal and thyroid glands play a more important part than any of the other endocrine organs in exerting some contra-insular or regulating mechanism by secretions opposing the activity of islet tissue. The thyroid gland may be overactive, with a relatively low basal metabolic rate ratio, in some of these cases of islet tumor, and with the removal of the tumor, a fatal thyroid storm or crisis may occur. We have had 1 death—1 of the 2 deaths in our cases of benign adenoma—from this cause, and 3 similar cases have been reported.

In every suspected islet tumor case, the basal metabolic rate should be determined, and if it is at all elevated—that is, with any reading over plus 15 per cent—operation should be delayed until the patient has been given a course of Lugol's solution, as in a case of toxic goiter.



We have made tissue cultures from 12 of the 34 tumors that we have removed. The tumor cells grow readily as epithelial sheets, as well as the connective tissue cells of the stroma. Early in our work, the idea occurred to us of transplanting the tumor cells, which had been grown in the plasma of a diabetic patient, into the areolar tissue of the axilla or groin of this patient. We have tried such transplantations in 4 severe cases of diabetes, with the hope and rationale that the physiologic demand of the patient, on cessation or reduction of insulin, would stimulate the islet-cells to grow and supply insulin. In none of the patients so treated, however, was there any evidence of growth or of decreased insulin requirement.

The surgical therapy and the procedures to be used for the removal of benign tumors, especially of the islet-cells, are now well recognized and accepted. In malignant tumors of the pancreas, and the ampullary area of the terminal common duct, the duodenum and pancreas surrounding the papilla of Vater, there is not the same agreement. The operative procedures now used have gone through, and are still going through, experimental stages, and a number of modifications of the radical removal of carcinoma in this area have been used.

In 1907 and 1908 two French surgeons, Desjardins (9) and Sauve (10), suggested radical operations with removal of the duodenum and ampullary area of the pancreas, but did not attempt them in humans. In 1912, Kausch (11) successfully performed a pancreaticoduodenectomy for carcinoma of the ampulla, doing the operation in two stages. His patient lived for nine months, but died of a cholangitis.

The use of a cholecystenterostomy and the routine use of catgut in these attempts resulted in hemorrhage, peritonitis, fistula and infection of the bile ducts in a prohibitive percentage, and further efforts were abandoned until 1935, when Dr. Parsons, Dr. Mullins and I reported our first radical procedure. I regret that we reported this first case, for it is quoted without references to the subsequent modifications and improvements which we have since published.

The use of Vitamin K pre-operatively to combat the bleeding tendency in deep jaundice, of Vitamin B and a high protein and carbohydrate diet before operation to repair liver damage, ample transfusion of blood, plasma and saline to maintain fluid and electrolyte balance, together with rigid silk technique in the operation—these have made the one stage radical procedure possible and preferable to the two stage method. Experience has demonstrated the following principles: 1. One stage procedure; 2. The necessity of silk or cotton technique with its connotation of minimum tissue damage and maximum hemostasis; 3. Anastomosis of the common duct to the end or side of the loop of jejunum. Ligation of the common duct results too frequently in a biliary fistula; 4. Anastomosis of the stump of the body of the pancreas to the same loop of jejunum; 5. Anastomosis of the antrum of the stomach to the same loop of jejunum below the two previous anastomoses; 6. The use of steel wire for through and through retention sutures; 7. The use of a sump drain for continuous suction for a day or two after operation or longer if leakage or fistula develops.

From many surgical clinics individual cases have been reported. But in five

clinics especially, a fairly large number of these radical operations have been done, 49 at the Mayo Clinic; 27 at the Billings Hospital, Chicago; 46 at the Columbia-Presbyterian Clinic; 49 at the Lahey Clinic and 22 at the New York Hospital—some 193 cases at the last reports from these centers. These figures include 16 total pancreatectomies, not all for carcinoma. The over-all post-operative mortality is still high, some 30.8 per cent, but these include all the early cases, and the operative risk has been steadily reduced in the last five years.

Dr. Waugh (12) from the Mayo Clinic reports 9 patients, one to three years after operation, with an average of two years. Dr. Brunschwig (13) reports 6 patients living from one to four years, the longest four years, back to normal activities. The series at the Presbyterian show six patients living from six months to seven years. The latter was the first one stage radical operation reported by the writer. She had a carcinoma of islet-cells in the head of the pancreas without symptoms of hypoglycemia. Unfortunately, at the present time, although as active as ever, this patient shows evidence of liver nodules.

Dr. Catell (14), of the Lahey Clinic, has had 49 resections with only eight postoperative deaths, 16.3 per cent, a very remarkable record. Half of these patients showed carcinoma of the ampulla, the rest in the pancreas, except for two carcinomas in the duodenum, two of the common duct. Forty two per cent are living; one patient is living 62 months; several over three to four years. Two-thirds of the operations were in two stages, the other third in one stage. Dr. Gardner Child (15) has recently reported a series of 22 such radical procedures, with an operative mortality of 27 per cent. One of these patients is living and well 51 months, another 42 months, and another 18 months.

At best the results are not brilliant, but some of these patients are given a life activity and expectancy, with freedom from pain, itching and jaundice that they could not otherwise have. As patients are diagnosed earlier and as the technique for the radical operations improves, the immediate and late mortality should show real improvement.

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# SUBTOTAL GASTRECTOMY IN THE TREATMENT OF CHRONIC RECURRENT PANCREATITIS\*

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The medical therapy of chronic recurrent pancreatitis has proved of little avail in controlling the symptoms or in altering the course of the disease.<sup>1</sup> Once the fully developed picture of chronic pancreatitis becomes evident, with severe abdominal pain, digestive distress, disturbances in fat and carbohydrate metabolism and resultant loss of weight and strength, conservative management has little to offer the patient. Therapeutic measures consist of a low fat, high protein diet combined with substitution therapy in the form of large doses of pancreatin. In many cases, because of the severe pain, unrelieved by analgesics, opiates are introduced and addiction develops.

In view of the failure of medical therapy, numerous surgical procedures have been carried out. These include cholecystectomy and T-tube drainage, anastomotic operations between the stomach and the small intestine, partial and total pancreatectomy, pancreatolithotomy and ligation of the pancreatic ducts, and sectioning of the sympathetic and parasympathetic nerve supply to the pancreas.

One of our patients, suffering from chronic pancreatitis for fourteen years, failed to obtain relief from cholecystectomy and T-tube drainage. Three years after this operation, he developed a gastric ulcer which we felt to be secondary to the decreased quantity and lowered alkalinity of the juice elaborated by his diseased pancreas. The resultant failure of neutralization of gastric acidity was considered to be causative in the formation of the ulcer. The ulcer was treated in the conventional manner and healed, as determined by radiography and gastroscopy, although symptoms did not disappear completely. A great deal of thought was given to the suggestion that, should the ulcer recur, a subtotal gastrectomy would be indicated. In addition to removing the ulcer, this operation would diminish the output of acid gastric juice and divert the flow of acid chyme through the gastrojejunostomy and therefore away from the duodenal mucosa. This in turn would reduce the hormonal phase of pancreatic secretion to such an extent that the pancreas would be partially inactivated. We hoped that, by splinting the pancreas in this way, relief of pain would ensue.

Accordingly, when the patient experienced no remission during the next year and the radiologist reported a recurrence of the gastric ulcer, subtotal gastrectomy was done. To our gratification, the patient experienced complete relief of pain and digestive distress and gained sufficient weight and strength to enable him to return to work for the first time in four years.

In view of this result, we are publishing a preliminary report of our experience.

## CASE REPORT

*First Admission.* (Adm. #569703) C. V., a bartender, aged 39 years, entered the Mount Sinai Hospital on October 1, 1941. For the past seven years he had been on a restricted

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diet and medication for a condition which he had been told was duodenal ulcer. Nine hours before admission, he had been seized with severe epigastric pain radiating to the back, accompanied by nausea, vomiting and extreme weakness. His usual medication had failed to give any relief and since the pain was becoming increasingly worse, he sought hospital care. In elaborating on his history, he stated that he had been treated for syphilis at intervals during the past five years, and that his last blood test, some months ago, had been negative.

On examination, the patient appeared acutely ill, pale and anxious. He was sweating profusely. Temperature was 101°F., pulse 72, respirations 22. Blood pressure was 120 systolic and 80 diastolic. There was considerable tenderness and rigidity in the epigastrium and right upper quadrant, but no rebound tenderness. Rectal examination was negative. Laboratory tests showed a white blood count of 10,600 with 71 per cent polymorphonuclears, 24 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophiles. The urine was negative for sugar and albumin. Electrocardiogram revealed no abnormalities. Blood sugar was 75 mg. per cent, urea nitrogen 16 mg. per cent and chlorides 595 mg. per cent. Blood amylase was equivalent to 400 mg. of sugar. Blood and spinal fluid Wassermann reactions were negative. Colloidal gold and globulin tests of the spinal fluid were normal. Total protein of the spinal fluid was 39 mg. per cent and the Pandy test was negative.

On conservative treatment, the pain subsided within a few hours, the patient's temperature dropped to normal and all signs of peritoneal irritation vanished. After the disappearance of acute symptoms, roentgenographic studies revealed no evidence of a gastric or duodenal ulcer, nor was any abnormality of the duodenal curve apparent. Gastric analysis after the gruel meal disclosed free acid to fifteen degrees and a total acidity of forty-four degrees. Oral cholecystography resulted in the visualization of a normal gallbladder which contained no stones. The fundus of the gallbladder was angulated on itself but this was not considered abnormal.

The patient was discharged on October 15, 1941 with a diagnosis of acute pancreatitis and referred to the Out-Patient Department for follow-up care.

*Second Admission.* He was readmitted to the hospital on May 7, 1942 with a four hour story of severe epigastric pain, nausea and vomiting. On examination, the patient was writhing in pain and perspiring and his skin was cold and clammy. Temperature was 100°F., pulse 90, respirations 20. There were no abnormalities in the heart and lungs. Blood pressure was 150 systolic and 88 diastolic. There was marked tenderness and rigidity in the upper abdomen. The lower abdomen was soft. Rectal examination was negative. Exploratory puncture in the lower abdomen revealed no free fluid. X-ray of the abdomen disclosed no free air under the diaphragm and no evidence of intestinal obstruction. Hemoglobin was 100 per cent, white count 13,400 with 66 per cent polymorphonuclears, 30 per cent lymphocytes and 4 per cent monocytes. Blood Wassermann was negative, urea nitrogen 20 mg. per cent, and chlorides 585 mg. per cent.

A clinical diagnosis of acute pancreatitis was made and the patient was treated by gastric intubation, intravenous fluids and chemotherapy. Temperature rose to a high of 102.8°F. on the fifth day and then dropped to normal as the patient's condition improved. He was discharged on May 17, 1942. On his follow-up visits, he continued to complain of pains and dyspepsia.

*Third Admission.* The patient was again admitted on July 31, 1942. He had been suffering for the preceding two days with mild upper abdominal pain, nausea and vomiting. He appeared acutely ill, but less so than on his previous admissions. There was some tenderness in the epigastrium, but no rigidity. After twenty-four hours, all symptoms and signs disappeared. Significant laboratory findings were a blood amylase equivalent to 410 mg. of sugar. A scout film of the abdomen showed no free air under the diaphragm. It was our impression that the patient had reached the end of a bout of acute pancreatitis and he was discharged on August 4, 1942, again to be followed in the Out-Patient Department.

*Fourth Admission.* On January 19, 1943, the patient returned with a three hour history of severe upper abdominal pain, nausea and vomiting. He was acutely ill and pale, sweating



profusely and very restless. Considerable tenderness and rigidity were present in the upper abdomen. Rectal examination disclosed some bogginess and tenderness over the anterior wall. Hemoglobin was 85 per cent, white count 19,650 with 92 per cent polymorphonuclears. Urobilinogen was present in a dilution of 1:20. Blood amylase was equivalent to 120 mg. glucose and rose to 350 mg. in twenty-four hours. Scout film of the abdomen revealed no free air under the diaphragm. After forty-eight hours, no definite improvement had occurred, and accordingly on January 21, 1943, exploration was undertaken by Dr. Colp.

At operation, the gallbladder was found to be normal in appearance, although slightly dilated. Both the gallbladder and common bile duct contained dark green bile. The liver was normal. Opening the gastrohepatic omentum revealed a markedly edematous pancreas. A small piece of pancreas was excised for biopsy, the incision being narrowed by one silk suture. The divided gastrocolic omentum was closed with interrupted sutures. A typical retrograde cholecystectomy was performed, the cystic duct and vessels being ligated separately with chromic sutures. The common duct was incised and a T-tube placed in for drainage. Pathologic examination of the specimen showed acute pancreatic necrosis and chronic inflammation of the gallbladder wall. No growth was reported in a culture taken from the bile and peritoneal fluid at the time of operation.

T-tube drainage of the common duct was maintained for seventeen days. Just before its removal, a cholangiogram was done with 20 per cent diodrast and revealed the duct to be patent. When morphine was administered at the time of injection of the diodrast, the sphincter choledochus closed, but there was no dilatation above it. No dilatation of the hepatic ducts or biliary radicles was present above the point of insertion of the tube, and the small intestine filled with the radio-opaque fluid.

The patient's postoperative course was stormy. He developed atelectasis of the lower lobe of the right lung. Temperature rose to 103.4°F. but eventually subsided. X-rays of the abdomen revealed no abnormalities. Electrocardiograms revealed semi-inversion of the T waves in Leads 2 and 3, and this was interpreted as due to mild coronary insufficiency. Subsequently, the T waves reverted to normal.

He was discharged on February 11, 1943. He was seen in Follow-up Clinic and the Out-Patient Department where he complained of mild pains, anorexia, weakness. He also noted easy fatiguability and by April 15, 1943, three months after his operation, he had lost fifteen pounds.

*Fifth Admission.* The patient returned to the hospital on July 21, 1944 complaining of severe, intractable epigastric pain for the past three days. At this time, he was acutely ill, although no more so than on any of his previous admissions. Temperature was 101°F. pulse 84, and respirations 20. Rectal examination was negative. Diffuse tenderness was present in both upper quadrants. No masses were felt. Hemoglobin was 83 per cent, white count 11,450, segmented cells 61 per cent, non-segmented 14 per cent. Blood urea nitrogen was 11 mg. per cent, blood sugar 80 mg. per cent, icterus index 4, blood amylase equivalent to 110 mg. of sugar. After 24 hours of intravenous therapy, all symptoms subsided and he was discharged.

He was seen more frequently in the Out-Patient Department. The tempo of his disease process was beginning to accelerate. He had been forced to stop work, he continued to lose weight and strength and in March 1945, he volunteered the information that for the past two weeks his stools were bulky, gray and foul smelling. Examination of the stool disclosed large, grayish brown, poorly formed masses which floated in water and from which an indescribably foul odor emanated. Large amounts of undigested muscle fibers and fat were seen microscopically. Chemical analysis showed a total fat of 48 per cent (normal 8 to 20 per cent).

*Sixth Admission.* Because of an incisional hernia which developed since the last admission, he again entered the hospital on April 4, 1945. While we were reluctant to expose him to another procedure, it was felt that in view of his comparative youth, a repair was warranted. This operation was refused by the patient and he was discharged on April 6, 1945.

*Seventh Admission.* He returned on September 9, 1945. The story was now quite familiar

to the patient and to us. He had not felt well since his last operation. In the Out-Patient Department, he continued to complain of pain, anorexia, bulky stools, weakness and weight loss. For two days prior to admission, he had had severe upper abdominal pain accompanied by nausea and vomiting.

He appeared to be in moderate distress. The abdomen was tense, but not distended. There was an upper right pararectus scar with separation of muscle borders in the midline. Rectal examination revealed a moderately enlarged prostate and some bulging in the cul-de-sac. Laboratory studies were as follows: Urinary amylase was 1024 units which dropped to 8 units in five days. Blood urea nitrogen was 14 mg. per cent, sugar 65 mg., cholesterol 178 mg., and total protein was 5.0 Gm. Cephalin flocculation test was negative. Alkaline phosphatase was 24 King-Armstrong units. Blood Wassermann was negative. On the fifth day, transient jaundice developed. The glucose tolerance was normal.

A plain film of the abdomen was taken and for the first time there was seen an irregular calcification to the right of the body of the third lumbar vertebra. The roentgenologist interpreted this calcification as due to stones in the region of the head of the pancreas.

Within a few days, symptoms cleared and he was discharged.

The patient was seen at regular intervals in the Out-Patient Department and, except for a few short periods of remission, he still complained of upper abdominal pains, anorexia, diarrhea and weakness. In August 1946, because of severe continuous pain for the preceding two weeks, x-ray examination of the gastro-intestinal tract was carried out and revealed a small ulcer on the posterior wall of the stomach, midway between the incisura and the cardia. Gastroscopy verified the presence of this ulcer. Hospitalization was advised but the patient postponed his admission for three months.

*Eighth Admission.* The patient was finally admitted to the hospital on November 7, 1946. For the first time, an attempt was made to obtain specimens of pancreatic juice after the administration of secretin. Unfortunately, whether because of spasm or lack of cooperation on the part of the patient, satisfactory intubation of the duodenum was not possible. In view of the presence of a gastric ulcer, it was deemed unwise to persist in attempting to pass the tube for fear of injuring the stomach.

The patient was placed on bed rest and a bland diet, and his pain disappeared. Gastroscopy was repeated and showed no evidence of the ulcer previously seen in the Out-Patient Department. X-ray examination of the stomach also showed that the ulcer had healed. The calcifications in the region of the head of the pancreas were again noted. Blood serum amylase was 86.5 mg. glucose per 100 cc. Blood sugar was 80 mg., cholesterol was 300 mg., with esters 170 mg. A glucose tolerance test resulted in normal findings (80, 90, 120, 110, and 80 mg.). Blood Wassermann was negative. Night Refhuss test disclosed free gastric acidity to be 32 degrees. The insulin test produced a gastric acidity of 56 degrees.

Since the patient had improved on medical treatment, operation was deemed unnecessary and he was again discharged. However, his pains recurred almost immediately and he was unable to work. Medical therapy consisted of a low-fat diet, pancreatin, antispasmodics, sedatives and vitamins but seemed to produce little relief. The stools were still grayish and bulky and contained a large amount of undigested muscle fibres. He lost a few more pounds in weight.

On August 15, 1947, again because of persistent epigastric pain for two weeks, another gastro-intestinal series was carried out. This revealed a gastric ulcer in the same location as previously. Gastroscopy confirmed the presence of this lesion.

*Ninth Admission.* He was admitted to the hospital on September 5, 1947. After the usual preparation, operation was carried out by Dr. Colp. An ulcer measuring 2 cm. in diameter was found on the posterior wall of the stomach, adherent to the pancreas, which was stony hard and nodular. The ulcer was freed from the pancreas, and a high subtotal gastrectomy was done. An ante-colic Hofmeister anastomosis was performed and the abdomen was closed.

The patient had a turbulent postoperative course. He developed atelectasis of the right

base followed by pneumonia. X-ray of the chest revealed marked elevation of the right diaphragm and for a time it was thought that a subphrenic abscess was developing. Temperature reached 104°F., and pain and dyspnea were severe. His course seemed to be similar to that following his cholecystectomy and choledochostomy in 1943. Blood culture taken on the eighth postoperative day revealed *B. coli*. Subdiaphragmatic paracentesis at varying levels yielded only but a few cubic centimeters of blood. Shortly after this, icterus developed. Blood chemical studies showed an icterus index of 50, cephalin flocculation one plus, and alkaline phosphatase 31 King-Armstrong units.

Intensive antibiotic therapy along with the usual supportive measures resulted in recession of the fever and sterilization of the blood stream. The lung signs cleared and the patient improved sufficiently to be discharged on October 9, 1947.

For the next several weeks, he complained of weakness, easy fatiguability and poor appetite. The usual symptoms we encounter after subtotal gastrectomy were absent: there were no epigastric distress, sinking feelings, faintness and flushing. Gradually he began to feel stronger, his appetite had improved and he stated that he had experienced none of the troublesome pain which had bothered him for the preceding eleven years. Triumphantly he reported that his stools were brown, and of normal size, shape and consistency. Examination of the stool substantiated this report: it was grossly normal stool and the total fat content was only 8 per cent.

He continued to feel well and at all subsequent visits he reported that he was free of pain.

Ten months after operation, this patient was found to be well. He stated that this is the only period of good health which he has enjoyed in the past fifteen years. There was complete disappearance of pain and digestive distress, and he has gained fifteen pounds. He has been working continuously for the past four months. Except for moderate restriction of fats and prohibition of alcohol, his diet is complete and he is receiving no medication.

The explanation of this dramatic result lies in an understanding of the physiology of pancreatic secretion. Pavlov<sup>2</sup>, after producing pancreatic fistulas in dogs, was the first to show that stimulation of the peripheral ends of the cut vagus and sympathetic nerves to the pancreas produced an outpouring of pancreatic juice. Babkin<sup>3</sup> and Mellanby<sup>4</sup> confirmed these results and demonstrated that this juice, although scanty, is rich in enzymes. Bayliss and Starling<sup>6</sup> in 1902 conclusively proved that an extract prepared by admixture of hydrochloric acid and duodenal mucosa, when injected intravenously, caused a copious outpouring of pancreatic juice in a dog whose pancreas had been denervated. They called this hormone so extracted "secretin." Other investigators have shown that the quantity of fluid and bicarbonate in pancreatic secretion is dependent on the production of secretin in the duodenum and upper jejunum.

In chronic pancreatitis of long standing, a large portion of the pancreatic gland tissue has been destroyed and replaced by fibrous tissue and calcification. Much of this fibrosis occurs around the pancreatic ducts and a great deal of calcium is deposited both within and around the ducts. Thus the ductal lumen is constricted and there is obstruction to the passage of pancreatic juice into the duodenum. The pain experienced by patients with chronic pancreatitis is caused by the interference with the flow of pancreatic juice through a duct which is blocked by stones and which cannot distend against unyielding fibrotic or calcified pancreatic tissue. If pancreatic secretion can be lowered to the point

where pressure within the ducts is lessened, pain will be relieved and, in effect, the pancreas will be splinted, thus tending to arrest the disease.

Rienhoff and Baker<sup>6</sup> performed sympathectomy and vagotomy in an intractable case of chronic pancreatitis, with results as satisfactory as in our case. The success of their procedure was based on interference with the nervous mechanism of pancreatic secretion. They felt that secretion of the denervated pancreas is decidedly reduced after severance of the autonomic nerve.

Our result is produced by minimizing the quantity of secretin brought to the pancreas. By doing a subtotal gastrectomy, the production of hydrochloric acid is lessened considerably. The reduced amount of hydrochloric acid produced by the stump of stomach is diverted through the gastro-enteric stoma into the upper jejunum and, while some acid may be formed here, it is minimal compared to the quantity one would expect after contact of a normal amount of hydrochloric acid with the duodenum. Diversion of hydrochloric acid from the duodenum by continuous gastric suction is used in acute pancreatitis to depress the secretin mechanism, thereby lessening the formation of pancreatic juice which can digest the pancreas and adjacent tissues<sup>7</sup>. In pancreatic fistula occurring after operations or trauma, large doses of sodium bicarbonate are given orally to replace alkali lost through the fistula and also to neutralize the gastric acidity. Secretin production is thus decreased and there is less pancreatic juice which might otherwise be lost through the fistula<sup>7</sup>.

A possible explanation for the improvement in fat digestion in our patient lies in the experimental work of Dragstedt<sup>8</sup> on dogs. He showed that removal of 80 to 90 per cent of the pancreas causes no defect in the digestion and absorption of food, provided that the pancreas remnant remains in connection with the duct and its secretion has free access to the upper intestine. These findings may be applicable in chronic pancreatitis in which a large part of the organ is functionless, and obstruction in the ducts has been relieved by the formation of a smaller quantity of pancreatic juice flowing under decreased pressure. This juice reaches the intestine without interference and is able to carry on the necessary normal digestion.

#### SUMMARY AND CONCLUSIONS

We have presented a case of chronic recurrent pancreatitis of fourteen years' duration in which the diagnosis was established by clinical, laboratory and operative findings. Following the development of a gastric ulcer, subtotal gastrectomy was done to remove the lesion and to alleviate the pancreatitis by interference with the secretin mechanism of pancreatic secretion. A dramatic cure resulted with disappearance of pain, steatorrhea, and creatorrhea. Gain in weight and strength were sufficient to permit the patient to return to work after eight years of disability.

Alleviation of the pancreatitis can be explained by the interference with the secretin mechanism of pancreatic secretion which resulted from diminution in acid output and diversion of the acid chyme from the duodenal mucosa into the



jejunum. The reduced quantity of secretin is responsible for formation of a lessened amount of pancreatic juice which flows under decreased pressure through pancreatic ducts which have been constricted and partially blocked by calcification and cicatrization. Thus, distention of the ducts does not occur and pain is not experienced.

Since the diminished quantity of pancreatic juice has free access to the intestine, digestion and absorption of food are carried on more efficiently than when there is obstruction to the flow. This accounts for the gain in weight and the disappearance of creatorrhea and steatorrhea.

We are, therefore, suggesting the operation of subtotal gastrectomy for chronic relapsing pancreatitis. This proposal is based on sound physiologic principles and, while experience with only one case limits our conclusions, we feel that the dramatic relief obtained in our case warrants repetition of this operation in other cases.

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# THE RELATIONSHIP OF PANCREATIC DUCT OBSTRUCTION AND DILATATION TO FAT NECROSIS OF THE PANCREAS<sup>1</sup>

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Although experimental studies concerning acute pancreatic necrosis have attracted much attention in the past, the exact nature and pathogenesis of this disease process still remain obscure. In 1855, Claude Bernard (1) attempted to reproduce this disease in dogs by injection of bile and sweet oil into the pancreatic duct. In 1899, Lancereaux (2) postulated the theory that reflux of bile into the pancreatic duct caused acute pancreatitis, and in 1901, Opie (3) described in detail such a case—a gallstone lodged in the ampulla of Vater, converting the common bile and pancreatic ducts into a common channel, with resultant reflux of bile into the pancreatic duct. With such an obstruction, in order for bile to flow into the pancreatic duct, the anatomic arrangement of the ducts must be such that conversion into a common channel is possible, and, furthermore, the relative pressures must be such that the direction of flow is toward the pancreatic duct.

Mann and Giordano (4), using 200 fixed specimens, found that in only 3.5 per cent did the anatomy of the ducts allow the development of a common channel when obstruction occurred at the papilla of Vater. Furthermore, many cases of pancreatic necrosis have been described in which the pancreatic and common ducts had separate openings into the duodenum, or in which the duct of Santorini drained the major portion of the gland. Many cases of pancreatic fat necrosis show at autopsy no stone or other obvious obstruction at the papilla of Vater. This latter objection was challenged by Archibald (5), who supported the belief that biliary dyskinesia may convert the ducts into a common channel. Further survey of the literature reveals that reflux of duodenal contents into the pancreatic duct has been implicated as a cause of pancreatic necrosis by some observers. For a long time it was believed that, because of the frequent association of chronic cholecystitis and acute pancreatic necrosis, infection played a major role, spreading from the diseased gall bladder to the pancreas via the lymphatics. Another group of observers suggested circulatory disturbance as a major etiological factor in acute pancreatic necrosis, but again this has not been universally accepted.

Since none of the above factors had been successfully implicated in the vast majority of cases of pancreatic necrosis, Rich and Duff (6) investigated the smaller pancreatic ducts in an effort to clarify this problem. These authors suggested, "The majority of cases of hemorrhagic pancreatitis result from partial obstruction to the outflow of the secretion, causing distention and rupture of acini and ductules behind the obstruction, with resultant escape of the pancreatic juice into the interstitial tissue." They believed that rupture of the dilated acini was particularly liable to occur during periods of increased tension within the

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pancreatic duct system, such as after a large meal or excessive alcohol intake. They expressed the view that in most cases the main pancreatic duct was not obstructed and that the obstruction was situated within the smaller radicles. They stated that metaplasia of the duct epithelium, leading to partial obstruction and consequent dilatation and rupture of the distal acini, was very frequent and they concluded, "It is our belief that this form of duct obstruction leading to acinar rupture and escape of secretion plays an important role in the pathogenesis of many cases of hemorrhagic pancreatitis, though any of the numerous causes of duct obstruction may, of course, lead to the same result."

Yotuyanagi, quoted by Lewison (7), after an exhaustive study of pancreatic duct metaplasia, found that it occurred normally in the human pancreas in at least 64 per cent of the specimens examined. They state, "This conspicuous frequency of ductule metaplasia in the normal pancreas is inconsistent with the infrequency of acute pancreatic necrosis." Nevertheless, the relationship between acute pancreatic necrosis and obstruction of the small pancreatic ducts, whatever the cause, still remains a disputed problem. It was with this in mind that the following study was undertaken.

It was felt that it would first be necessary to describe the usual appearance of the small pancreatic ducts and acini. Accordingly, 100 microscopic sections of pancreatic tissue were examined, with the results shown in Table I.

TABLE I

*The microscopic appearance of the small ducts and acini in 100 consecutive routine pancreatic sections*

1. Number of cases with completely normal appearing ducts and acini.....	82
2. Number of cases with slight dilatation of small ducts and acini.....	14
3. Number of cases with marked dilatation of ducts.....	4

In this and all subsequent studies, microscopic sections stained with hematoxylin-eosin were used, and two or more sections examined in each case. Table I shows that in 82 per cent of the specimens there was a normal appearing pancreatic duct system. In 14 per cent, slight dilatation was present, and in 4 per cent, the dilatation was marked. It was noted during this study that secretion was frequently seen within the ducts; the amount seen was frequently, though not invariably, related to the degree of duct dilatation, as shown in Table II.

TABLE II

*The amount of pancreatic secretions present within the pancreatic duct system in 100 consecutive routine pancreatic sections*

1. Number of cases with no duct dilatation, with a small amount of secretion present in the moderate sized or larger ducts.....	18
2. Number of cases with no duct dilatation, with a marked amount of secretion present in the larger ducts.....	3
3. Number of cases with slight small duct dilatation, with moderate amount of secretion present in all the ducts.....	14
4. Number of cases with marked dilatation of all ducts with marked amount of secretion throughout.....	2

Thus, in this material, there were, occasionally, varying amounts of secretion within the moderate-sized and large ducts, without apparent duct dilatation or other obvious cause.

Since it was stated by Rich and Duff that small duct dilatation with rupture of distal acini caused the majority of cases of pancreatitis, twenty-three sections with varying degrees of duct and acinar dilatation, without fibrosis, were examined to discover the possible effects upon the pancreatic parenchyma. In nine cases, there was moderate dilatation of the small duct system, and in 14 the dilatation was extreme. Among these cases, three showed fat necrosis, all among the group with extreme dilatation. The fat necrosis was extensive in the first case, moderate in the second, and minimal in the third. It is noted in Table II that in some cases, although there is no dilatation of the duct system, there are varying amounts of pancreatic secretion within the lumina of the moderate- and large-sized ducts. It was felt at that time that perhaps this stasis played a role in the development of fat necrosis, but none of the cases with moderate to abundant secretion stasis showed any evidence of fat necrosis.

If the duct and acinar obstruction and dilatation were important etiological factors in the development of pancreatic necrosis, one would expect to find evidence of such obstruction in a great many cases showing fat necrosis. Accordingly, 35 such pancreatic sections were examined; the results are presented in Table III.

TABLE III

*Extent of small duct and acinar dilatation in 35 cases revealing pancreatic fat necrosis*

I. Moderate fat necrosis .....	20
a. Absence of duct or acinar dilatation .....	14
b. Moderate small duct dilatation .....	4
c. Marked small duct dilatation .....	2
II. Extensive fat necrosis .....	15
a. Absence of duct or acinar dilatation .....	9
b. Moderate small duct dilatation .....	5
c. Marked small duct dilatation .....	1

Thus, among 35 cases of fat necrosis, twelve had moderate to marked small duct and acinar dilatation. It can be seen that these changes are definitely more frequent when fat necrosis is present, as compared to routine pancreatic sections, suggesting an etiological relationship. Among all 35 cases of fat necrosis, however, only three had marked duct and acinar dilatation, and in nine the changes were moderate. In the remaining 23 specimens the duct-acinar system was completely normal. It is possible, therefore, that in a limited number of cases of pancreatitis small duct obstruction plays an etiological role, but there is insufficient evidence in this material to explain most cases on this basis.

#### CONCLUSIONS

1. Among 100 consecutive pancreatic microscopic sections studied, 18 revealed some degree of small duct and acinar dilatation and 37 revealed varying amounts of pancreatic secretion within the duct system.

2. Among 23 pancreatic sections with moderate to severe dilatation of the small duct and acinar system, three showed evidence of fat necrosis.

3. Among 35 sections with moderate to severe fat necrosis, three revealed marked small duct dilatation, and nine showed moderate dilatation.

The majority of cases of fat necrosis in this series could not be explained on the basis of obstruction of the smaller pancreatic ducts, with distal rupture of ductules and acini, causing liberation of pancreatic juice into the interstitial tissue.

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## INSULIN RESISTANCE IN DIABETIC KETOSIS

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Since the introduction of insulin in 1922, there has developed a considerable literature on insulin-resistance (1-43, 45, 47, 49, 52, 53). It is the purpose of this paper to report one such case. For comparison, all available cases of diabetic ketosis treated at The Mount Sinai Hospital in the past twenty years will be reviewed. We shall also suggest a possible mechanism for insulin resistance in the light of recent experimental work.

### CASE REPORT

A. G., white, Austrian-born housewife, aged 65 years, entered The Mount Sinai Hospital for the third time in August, 1946. Her first admission in June, 1942 was for treatment of a severe laceration of her leg. It was found then that she had been a known diabetic for the previous ten years, with the diabetes having been satisfactorily controlled with a daily injection of 80 units of protamine zinc insulin. On this regimen she usually "spilled one to two plus sugar." The wound healed satisfactorily within a week and she left the hospital.

Her second admission was in February, 1944. During the preceding two years insulin dosage had been reduced to 24 units of protamine and 25 units of regular insulin each morning. Three days before this admission, she developed diarrhea and anorexia, for which reason she did not take insulin. On the evening before admission she experienced weakness, vertigo, polydipsia and polyuria. At the hospital she was found to be well oriented; there was an acetone odor to her breath and occasional singultus. There was moderate anemia and the urine revealed 4 plus sugar and 4 plus acetone. The blood sugar was 500 mg. per cent, the CO<sub>2</sub> combining power was 23.2 vol. per cent, and the blood urea nitrogen was 8 mg. per cent. She was treated with the intravenous administration of 500 cc. of physiological saline (first five hours), followed by 5 per cent glucose in saline, and regular insulin to a total of 220 units in the first nine hours, at the end of which time her urine was sugar and acetone free. She was then placed on a regular diet and protamine zinc insulin, which was gradually increased from 35 to 50 units each morning. On this regimen she spilled 6 to 12 grams of glucose-equivalent daily.

She reentered the hospital in August, 1946 after five days of nausea, anorexia, and vomiting. Because of these symptoms she had reduced her insulin intake. On admission, she was overactive and incoherent. She appeared dehydrated, her pharynx was injected and there was an acetone odor to her breath. There was a moderate anemia and leucocytosis with a shift to the left. The urine showed 4 plus sugar, 4 plus acetone and 1 plus diacetic acid. The blood urea nitrogen was 10 mg. per cent, sugar 480 mg. per cent, chlorides (as sodium chloride) 544 mg. per cent, carbon dioxide combining power 25 volumes per cent. She was immediately given 100 units of regular insulin and an intravenous infusion of physiological saline. Insulin in large doses was repeated at frequent intervals. At the end of eight hours, she had received 740 units of regular insulin without showing any clinical improvement or change in the urinary findings. The intravenous fluid was then changed to M/6 lactate solution. During the following six hours, she received four liters of this solution and 1120 units of regular insulin, half intramuscularly and half subcutaneously (a total of 1860 units of insulin in the first thirteen hours of treatment). At this time, the urine showed 3 plus sugar, 1 plus acetone, and no diacetic acid. The blood sugar was now 270 mg. per cent and carbon dioxide combining power 54 volumes per cent. The intravenous fluids were then changed to 5 per cent glucose in saline. During the next three hours, she

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continued to excrete 2 to 4 plus sugar; she became acetone free on an additional 120 units of regular insulin and 1700 cc. 5 per cent glucose in saline intravenously (thiamin, riboflavin, and nicotinamide were also administered intravenously). Five per cent glucose in saline and frequent small doses of insulin were continued for another six hours during which time the urine became also sugar free. During these six hours she thus received an additional 70 units of insulin and 1250 cc. of 5 per cent glucose in saline. The total for the twenty-four period was 2150 units of regular insulin. She now appeared well, despite a transitory rise of temperature to 102° F. She was well oriented, able to take food, and displayed no signs of insulin shock. She remained asymptomatic and excreted no sugar or acetone despite the ingestion of food and the withdrawal of insulin for 66 hours. On the morning of the fourth hospital day, she became again incoherent, excited, and excreted 4 plus sugar and 4 plus acetone. The blood sugar was found to be 520 mg. per cent and the carbon dioxide content 11.2 volumes per cent. She was promptly given 200 units of regular insulin and in the course of the first three hours she received a total of 700 units of insulin subcutaneously without showing improvement clinically or in the urinary findings. An intravenous infusion of physiological saline was then instituted and 200 units of insulin were administered subcutaneously, and this was followed by smaller doses hourly. Eleven hours after the therapy of her second ketotic episode was initiated, she appeared improved, the urine revealed 4 plus sugar but there was no acetone. During these eleven hours, she received a total of 2250 units of insulin. During the following seven hours, she received 1200 cc. of 5 per cent glucose in saline, 25 units of insulin and food by mouth (*ad lib.*). Three hours after the last dose of insulin the urine was sugar and acetone free; the blood sugar was now 100 mg. per cent. On the following day the urine remained essentially sugar free on a total of 70 units of regular insulin in divided doses. One day later, she spilled 3 to 4 plus sugar and no acetone. An insulin tolerance test was attempted. Six hours after the last dose of insulin, on a fasting stomach, 10 units of regular insulin were administered subcutaneously. At the beginning of the test the blood sugar was 390 mg. per cent, one half hour later, 370 mg., per cent and one hour later, 280 mg. per cent. She received 80 units of regular insulin in the course of that day and was allowed out of bed on an unrestricted diet. The following day she was started on protamine zinc insulin, 30 units. She required an additional 50 units of regular insulin. During the succeeding week that she remained in the hospital on an unrestricted diet, she was maintained on 30 units protamine zinc insulin alone, spilling 2 to 3 plus sugar in the afternoon. At the time of discharge she was in good physical condition. Subsequently when seen in the out-patient department, the insulin was changed to 20 units of protamine zinc insulin and 20 units of regular insulin each morning. On this dosage, she spilled one to two plus sugar in the afternoon and her fasting blood sugar was maintained between 100 and 125 mg. per cent.

#### DISCUSSION

In order to compare this with others that were treated at the Mount Sinai Hospital, we reviewed the charts of 111 admissions of 80 patients for diabetic acidosis, which represent all charts available for the period between 1926 and 1946. Some of the data are presented in table I.

As is apparent from the table, we were unable to establish a relationship between the insulin requirement in diabetic ketosis and the initial blood sugar, such as found by Root (47) in his much larger series. The range and the average blood sugar levels were essentially the same for all dosages of insulin required. Similarly, the duration of acidosis under hospital observation did not vary significantly with the insulin requirement. The average carbon dioxide combining power did vary, in a very rough manner, inversely to the amount of insulin required to make the urine acetone free. However, the range, here too, was so wide as to limit its

value as a guide to insulin dosage. It must be concluded that the therapy of diabetic acidosis cannot be generalized, and that each case must be treated in accord with the clinical condition and the urinary acetone and sugar changes.

At The Mount Sinai Hospital, the usual procedure in treating diabetic acidosis is to provide fluids intravenously (either physiological saline or 5 per cent glucose in saline) and to give insulin subcutaneously (and occasionally intravenously) at frequent intervals, using the urinary changes as a guide. Blood is drawn on

TABLE I

TOT. INS. RE- QUITED*	NO. OF ADM.	REMARKS	DUR. OF ACIDO- SIS HRS.*		INITIAL BLOOD SUGAR MG. $C_0$	AVER- AGE BL. SUG. MG. $C_0$	CO <sub>2</sub> COMB. POWER VOL. $C_0$	AVER. CO <sub>2</sub> COMB. POW. VOL. $C_0$	INITIAL DOSE INSULIN	INSULIN TOTAL 1ST 3 HRS.
			Range	Aver- age						
2250	1	Our pt.	11		520		11		200	700
1980	1	Out pt.	18		480		25		100	200
1460	1		16		360		19		25	200
800-1000	3		10-18	14	300-600	487	6-28	15	50-100	100-600
400-800	9	1 death†	6-36	12	260-540	369	11-42	24	30-250	95-640
200-400	24	2 " ‡	4-48	21	290-600	397	7-44	22	10-150	20-250
100-200	30	1 " §	3-40	14	180-500	351	11-39	25	20-100	30-150
10-100	44	7 "	1½-34	11	200-560	350	11-47	32	5-50	10-90
10-100	37	omitting 7 deaths	1½-34	11	200-560	330	11-47	34		

\* From admission until urine acetone-free.

† Died of pneumonia 5 days after diabetic acidosis corrected.

‡ 1) Died of appendiceal abscess and peritonitis one week after acidosis controlled.

2) Died of myocardial infarction on second day (admitted for acidosis and coronary occlusion).

§ Died of pneumonia and circulatory collapse three days after acidosis controlled.

|| 1) Died of pyelonephritis and bronchopneumonia 9 days after acidosis controlled.

2) Died of endothelioma of cerebral dura 12 hours after admission, at which time urine acetone free 7 hours.

3) Died of influenzal bronchopneumonia 5 hours after admission, acidosis responding to therapy.

4) Died of coronary thrombosis, 2½ hours after admission, urine acetone free.

5) Died two days after control of acidosis with hyperpyrexia and clinical picture of cerebro-vascular accident.

6) Died of diabetic ketosis complicated by thyrotoxicosis 8 hours after admission. B.S. 480, CO<sub>2</sub> 11 on admission. Total insulin 80 units plus intravenous fluids.

7) Died of diabetic coma, 3½ hours after admission. B.S. 560. Received 70 units insulin plus repeated injections 50 per cent glucose in water intravenously (1928).

admission for sugar, CO<sub>2</sub> combining power, urea and chlorides, but, as demonstrated in the Table, the results seem to be of limited value as a therapeutic guide.

Among the 80 patients whose 111 admissions were reviewed, there were 11 deaths. Of these, 6 died of infections or vascular accidents two or more days after the diabetic ketosis had been controlled. Of the remaining five, who died within twelve hours after admission, three were acetone free at the time of death,

and death was ascribed to influenzal bronchopneumonia, a cerebral meningioma and coronary insufficiency, respectively. In the two remaining cases death seems to have been due to diabetic coma. One of these, a 56 year old man with an initial blood sugar of 560 mg. per cent died  $3\frac{1}{2}$  hours after admission. During this period he received 70 units of insulin and repeated intravenous injections of 50 per cent glucose in water, the approved therapy at that time (1928). The other patient, a 53 year old man with an initial blood sugar of 480 mg. per cent and a carbon dioxide combining power of 11 volumes per cent, died eight hours after admission, having received during that period 80 units of insulin, 500 cc saline in the first five hours and 400 cc 5 per cent glucose in saline during the last three. Thus, in both cases in which death may be attributed to acidosis, insufficient insulin seems to have been administered.

In the case herein reported the unusual insulin requirement could hardly be anticipated, since she had been previously so well controlled on relatively small doses of insulin and demonstrated a significant response in blood sugar even to a small test dose of insulin (10 units), after control had been established. It is tempting to speculate about the pathogenesis of the marked insulin resistance shown by this patient during the two episodes of diabetic ketosis. In the light of Cori's (46) demonstration of the inhibition by insulin of anti-hexokinase factors in the pituitary and adrenal cortical secretions, it is our opinion that the insulin withdrawal to which our patient subjected herself (and which we inadvertently repeated) permitted a large excess of these hormones to accumulate. The concentration of anti-hexokinase factors was probably increased by the pituitary and adrenal cortical response to the "alarm reaction" (48) provoked by the ketosis, dehydration, and salt loss. Consequently, a very large amount of insulin was required to "neutralize" the anti-hexokinase substances, before carbohydrate utilization could again proceed.

Price, Cori and Colowick (51) were able to quantitate the cortical extract anti-hexokinase neutralizing effect of insulin: 50  $\Gamma$  of insulin counteract 0.1 cc. of Upjohn cortical extract. The insulin requirement therefore is dependent on the anti-hexokinase excess (which the available chemical tests do not determine) rather than of the degree of acidosis or of the blood sugar level. This suggests that the determination of the insulin-neutralizing titer of the patient's freshly drawn blood, using the mouse as a biologic indicator, might prove more satisfactory as a guide to insulin dosage in diabetic ketosis than the chemical tests in common use.

Himsworth's (29) observation that the arterio-venous glucose difference in insulin-resistant patients is much lower than in patients with normal insulin sensitivity, provides evidence for the existence of circulating anti-hexokinase (or anti-insulin) substances. Furthermore, Watson and Dick (31) demonstrated insulin inactivating substances in the urine of diabetics. Support for the suggestion that these substances may accumulate is gained from the common observation that the insulin requirement in diabetic ketosis increases with the duration of acidosis. In Felder's (44) case of chronic insulin resistance which developed following gangrene of the leg ("stage of resistance" of Selye, since the patient was

adapting over a long period), he noted that the insulin-inhibitory effect of the patient's serum, as tested by protection against insulin shock in mice, was much greater when insulin had been withheld for 24 hours before blood was drawn than when insulin had been given freely up to the time of the experiment. Here then, we appear to have an example of accumulation of an anti-insulin substance which could be prevented by continuous "neutralization" by insulin.

Hyperglycemia during the "alarm reaction" is a well known phenomenon. Its duration speaks against the usually ascribed etiology of hyperadrenalism as the sole cause in many cases. In a series of 144 cases of trauma of all types, Thomson (49) found impaired carbohydrate tolerance in 63 per cent, lasting up to a month, with an average duration of 15 days. Albright (50) refers to the case of Col. Adamson who, after prolonged exposure on a life raft in the Pacific, developed severe diabetes which later disappeared. Selye (48) noted hyperglycemia in rats exposed to continuous severe cold for the first 24 hours and then again from the third to the 16th days.

Insulin, as pointed out by Lerman (39), is a poor antibody producer, but when such antibodies are formed they are true antihormones. Although this anti-hormone formation may be a factor in some cases of insulin resistance, it is unlikely that it played a role in our case; there was no evidence of allergic reaction and in the intervals between ketosis the patient responded to small doses of insulin.

It seems not improbable that insulin resistance in diabetic ketosis, shown to an extreme degree in our case, is due to the excessive production and accumulation of pituitary and adrenal cortical hormones which must be "neutralized" by insulin before carbohydrate metabolism can normally proceed.

#### SUMMARY

A case of diabetes mellitus, requiring over 2000 units of insulin on two separate occasions of acidosis three days apart, is described.

A series of 80 patients with diabetic acidosis treated at The Mount Sinai Hospital, New York, between 1926 and 1946 is reviewed.

No relationship could be found between the initial blood sugar and the insulin requirement for control of acidosis.

It is suggested that insulin resistance may be due to the excessive production and accumulation of pituitary and adrenal cortical hormones which requires "neutralization" by insulin before carbohydrate metabolism can proceed.

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## SOLITARY MYELOMA OF A RIB\*

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Under the term "solitary myeloma," as used in the literature, are included all cases of single myeloma—those which have remained the sole lesion throughout their entire period of observation as well as those which developed multiple lesions after varying time intervals. A review of the literature reveals only a small number of solitary myelomas which have been proven "truly solitary" by an extended period of observation or by a complete detailed post-mortem examination.

It has been stated that if seen early enough, all cases of multiple myeloma would be found to start as a solitary focus from which all the other lesions are metastatic. The large number of cases of multiple myeloma which are seen clinically as compared with the small number of cases which have their onset as a solitary lesion would tend to negate this view.

It must not be forgotten that multiple myeloma is basically a disease of the bone marrow, and that the osseous manifestations are secondary. In fact Tranbøl has reported that the disease may be confined entirely to the marrow and have no demonstrable skeletal lesions.

It seems more logical to consider the solitary type as a benign form of myeloma, not only because in some instances it remains solitary over a long period of time, but also because in many of those cases which later become generalized the disease process appears to run a slower course than the malignant type of multiple myeloma. In this respect it must not be overlooked that although the average duration of life in multiple myeloma is two to three years, there have been cases reported wherein the period of observation was as long as fourteen years (Batts).

The question also arises as to how long a solitary myeloma must be followed in order to be assured that generalization will no longer occur. A number of cases have been reported in which generalization occurred four to five years after the onset of the original tumour. A case of myeloma of the maxilla, as reported by Gross and Vaughan, did not become multiple until nine years after its original appearance. There is the possibility that this lesion arose from the mucous membrane of the mouth or antrum, and, therefore, cannot be classified with certainty as a solitary myeloma of bone.

In 1928, Geschickter and Copeland collected all the known cases of myeloma and stated "In only five cases has the disease been found with a single focus and in all of these cases autopsy was not performed nor thorough roentgen ray studies made." In 1936, Cutler, Buschke and Cantril collected twelve cases of solitary myeloma from the literature (they discarded two of Geschickter and Copeland's five cases), added five from the Bone Registry of the American College of Surgeons, and one of their own. Of these eighteen cases, five had become generalized under observation, and in seven cases, the period of observation was less than eighteen months.

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In fact, in 1938, Bichel and Kirketerp, in a very critical analysis of the literature, would only accept two of the above cases as certain and three as probable ones in meeting the requirements for solitary myeloma. These authors believe that a sternal marrow examination must be negative in order to exclude a generalized myelomatosis. They cite two cases of solitary myeloma in which the x-ray examination of the entire skeleton was negative, but in which the sternal marrow showed that the lesion was only part of a generalized bone marrow disease. In their review, Bichel and Kirketerp accepted the cases of Shaw, Rogers, Harding and Kimball, Charbonnier and Mermod, and Case No. 18 of Cutler et al, from the Bone Registry of the American College of Surgeons. They may have been hypercritical in rejecting the cases of Rosselet and Decker, Bailey, and Cutler's Case No. 16. They did not accept this last mentioned case because the post-mortem examination of the skeleton did not include microscopy. Their rigid criteria for the diagnosis of a solitary myeloma are: a definite pathological diagnosis, a negative sternal marrow examination, and a long period of observation without the occurrence of generalization, if the patient were alive at the time of the report, or a microscopic examination of the entire skeleton if death had occurred. If one adheres to these criteria, solitary myeloma is indeed a very rare disease.

Besides the cases collected by Bichel and Kirketerp and Cutler et al up to 1938, cases of solitary myeloma of the facial bones had been reported by Stewart and Taylor, Gross and Vaughan, and Cappell and Mathers. As was stated previously, myelomas arising in this situation may have their origin from mucous membrane and should not be included in a discussion of myeloma of bone.

A case reported by Stewart and Taylor in 1932 was not included in any of the above series. A farmer, age 34, had pain in his right humerus in August, 1923, and sustained a pathological fracture of that bone four months later. X-ray examination showed a tumour of the upper end of the humerus. A forequarter amputation was performed and the patient was alive and well eight years later. The pathological examination revealed the tumour to be a plasma cell myeloma.

Other earlier cases reported by Ewald, Finzi, Mancini and Cabot (1938) must be discarded because the period of observation was of too short a duration.

Since 1938, approximately twenty-five publications on the subject of solitary myeloma of bone have been found in the literature. Of the cases reported in this literature, a number became generalized while still under observation (King, Aegerter and Robbins, Tennent, Abel, Toth and Wintermantel). Others have been followed for a very short period of time (Esposito, Leedham-Green et al, Paul and Pohle, Schwartz, Ferrandu and Guidotti, Cabot (1940) and Kamman).

In 1938, Vihvelin reported a case in which a myeloma of the vertebra had been diagnosed by operative removal twelve years previously. Although the tumour had recurred and had spread to adjacent vertebrae, there had been no generalization. In the same year, Scheinker, in a discussion of the effect of myeloma upon the nervous system, described a case of solitary myeloma of the sternum, with marked polyneuritic symptoms and skin changes. The patient was followed for one year. No other tumours were found either during life or at post-mortem examination, in which, unfortunately, only the vertebrae were examined.

In 1939, Batts, in a review of forty cases of multiple myeloma, cited two cases which began with solitary lesions and later became generalized. He also mentioned one case of solitary tumour in a patient who was alive fifty-nine months after the onset of symptoms, with no evidence of multiple lesions. Unfortunately, he does not mention the bone involved nor give any further data. Also in 1939, Pasternack and Waugh published the report of a patient who had a pathological fracture of the left humerus in January, 1930. The remainder of the skeleton was negative on x-ray examination. Radiotherapy was given, and callus formed. In November, 1936, an amputation was performed and a plasma cell myeloma was found on pathological examination. In March, 1938, eight years after the onset, examination of the urine showed no Bence Jones protein and the skeleton showed no other foci on x-ray examination.

In 1941, Tilden cited a case of solitary myeloma of the frontal bone which had been present for four years before partial excision was performed. This was followed by a course of radiotherapy. One year later, the patient was well and x-ray examination of the skeleton showed no other lesions. Willis reported a post-mortem examination on a patient who had a history of compression of the spinal cord for twenty years. A plasma cell myeloma of the second cervical vertebra was found. There were no lesions in any of the other bones examined. Also in this year, Tavernier and LeClere reported a myeloma of the scapula, which was proven by biopsy. Radiation was given and there were no "metastases" to be found three years later.

Brunner, in 1943, described a myeloma of the humerus which was curetted, and the patient was alive and well three years later, with no evidence of generalization.

In 1945, Kaufman cited an isolated myeloma of the skull of a boy, fourteen years of age. Excision was performed and radiation then given. The sternal marrow was examined and found to be negative. There was no Bence Jones protein in the urine. The patient was observed over a period of four years and there was no evidence of recurrence or distant lesions. Gootnick collected fifty-nine cases of solitary myeloma from the literature and added two well-authenticated cases of his own. These were situated in the right ilium, proven by examination of a biopsy specimen, and treated with radiotherapy. The one patient was alive and well four years after onset, with negative skeletal x-rays. The other showed no evidence of generalization, but died four years later from a carcinoma of the prostate. The sites of the sixty-one cases collected by Gootnick are: vertebrae, sixteen; ilium, thirteen; femur, nine; humerus, nine; skull, five; maxilla, three; clavicle, scapula, sternum, tibia, pubis, and sacrum, one each.

The only cases of solitary myeloma of a rib which could be found in the literature were two reported by Janes in 1939. Both tumors were completely excised. In one case generalization occurred eighteen months later, and in the other, death occurred post-operatively, and no autopsy was performed. Gruneis, in 1937, described a "probable" solitary myeloma of a rib, but the patient died a few weeks after its discovery and post-mortem examination revealed multiple foci.



The case reported here did not show any clinical or roentgen evidence of generalization in a three and one-half year period of observation from the time of onset to sudden death from coronary thrombosis. Unfortunately, no post-mortem examination was performed.

#### CASE REPORT<sup>1</sup>

*History.* M. S. (Adm. # 522904), a white male, fifty-eight years of age, was admitted to the Medical Service of Dr. Isidore Snapper at The Mount Sinai Hospital, on July 19, 1944, with a chief complaint of pain in the right arm, shoulder, and neck of six months duration. For six months prior to admission, the patient had suffered from a pain in his right shoulder, radiating down his arm and into his neck. He had been under the care of a number of physicians and had received various ineffectual treatments, until an x-ray examination of the chest showed a tumour of the right third rib. For five weeks before admission he had had a slight cough with occasional white mucoid sputum.

Twelve years previously he had pneumonia and six years before admission had developed a colitis, with seven to fifteen bowel movements daily. This had persisted for three years, but for the last three years, on a dietary regime, he had been asymptomatic. Three years prior to admission a hemorrhoidectomy was performed.

*Examination.* Physical examination on admission was essentially negative. There was slight tenderness over the upper right ribs posteriorly. Blood pressure was 170 systolic and 90 diastolic. Laboratory examinations revealed a markedly positive Sulkowitch test for calcium in the urine, but no Bence Jones protein was found. Examination of the blood showed a total protein of 7.5 per cent; albumin, 4.5 per cent; and globulin, 3 per cent. Alkaline phosphatase was fourteen King Armstrong units, and urea nitrogen was 9 mg. per cent. Sternal marrow aspiration showed a slight decrease in normoblastic elements with a low total nucleated cell count. No plasma myeloma cells were found. An electrocardiogram showed a left axis deviation; RT<sub>1</sub> and <sub>2</sub> depressed, T<sub>1</sub> and <sub>2</sub> diphasic; T<sub>4</sub> high, indicative of enlargement of the left ventricle and myocardial damage.

An x-ray examination of the chest showed a "destructive lesion involving the third rib, associated with a large soft tissue mass." The x-ray examination of the dorso-lumbar spine showed a moderate degree of hypertrophic spondylitis and a slight degree of osteoporosis, which was consistent with the age of the patient. An x-ray examination of the long bones showed no evidence of tumour, and examination of the kidneys showed them to be normal in size and position. An attempt to obtain some tissue, for pathological examination, by aspiration biopsy was unsuccessful. In order to determine whether the rib destruction might be due to direct extension from a peripheral pulmonary neoplasm, an artificial pneumothorax was induced. On roentgen examination a small adhesion was seen between the lung and the chest wall in the vicinity of the involved rib. Bronchoscopic examination was negative.

*Course.* Since no definite diagnosis could be established, it was decided to explore the tumour. The patient was transferred to the Surgical Service and on August 16, 1944, under intratracheal anaesthesia, a large tumour mass involving the third rib was found. A section of the fourth rib was excised, and the pleural cavity entered. Some thin pleural adhesions were found underneath the fourth and fifth ribs, but the lung parenchyma was not in contact with the tumour. The second and third ribs were cut across anteriorly and posteriorly well beyond the limits of the tumour and this entire section of chest wall removed *en masse*. The lung was palpated and no abnormality could be felt. The scapula was placed over the chest wall defect, the musculature sutured and the skin closed. The post operative course was uneventful. A small pleural effusion resorbed spontaneously. The pathological examination of the tumour revealed it to be a myeloma.

<sup>1</sup> This case has been referred to in Diseases of the Chest. Eli Rubin, M.D. Phila., W. B. Saunders & Co., 1947, p. 522.



Following this report, the urine was again examined for Bence Jones protein, and none was found. Sternal marrow aspiration revealed a slight increase in segmented elements, but no pathological cells. Re-examination of the spine showed no evidence of bone involvement. The patient was discharged on September 3, 1944, and readmitted for further study on September 13, 1944. Urine analysis was again negative for Bence Jones protein. The euglobulin and formol-gel tests were negative. Total proteins were 7.3 per cent; albumin, 4 per cent; globulin, 3.3 per cent; and the alkaline phosphatase remained the same as on the previous admission. Bone marrow examinations showed no change from the original findings. He was discharged on September 17, 1944, and when next seen on December 5 1944, he had gained twenty pounds and had no complaints.

He was readmitted to the hospital on November 14, 1945, with a virus pneumonia, from which he made a rapid recovery. Blood examinations at this time revealed the urea nitrogen to be 14 mg. per cent; cholesterol, 266 mg. per cent; phosphorus, 1.4 mg. per cent; total protein, 7.8 per cent; calcium, 8.8 mg. per cent; and alkaline phosphatase, 9 King Armstrong units. An x-ray examination of the chest showed the partial resection of the second, third, and fourth ribs on the right side but no other abnormalities. X-ray examination of the long bones, skull, spine and pelvis showed no evidence of myeloma. He was discharged on November 30, 1945.

He was seen in the Follow-Up Clinic on January 7, 1947, at which time he was well and had no complaints. An x-ray examination of the entire skeleton showed no change since the examination of November 16, 1945. Another sternal marrow puncture was performed and no abnormal cells were found in the smear. Blood proteins were normal. In July, 1947, he died suddenly from a coronary thrombosis, without having any symptoms suggestive of generalization of the myeloma. Unfortunately, no post mortem examination was performed.

#### SUMMARY

1. The literature on solitary myeloma of bone is reviewed.
2. A case of solitary myeloma of a rib in which excision was performed is reported. The patient died from coronary thrombosis, three and one-half years after the onset, without clinical, hematological or radiological evidence of multiple myeloma.

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## INFLUENCE OF 2-HYDROXYSTILBAMIDINE ON THE COURSE OF MULTIPLE MYELOMA

I. SNAPPER, M.D.\*

Stilbamidine has a favorable influence upon the pains of patients with multiple myeloma (1), but unfortunately relapses occur frequently. The dosage of stilbamidine should in general not exceed 2.5 Gm. Otherwise, the trigeminal neuropathy, which develops two months after the stilbamidine injections are terminated, becomes very severe.

We have been able to follow one patient with multiple myeloma who was treated with a large dose of stilbamidine which ultimately amounted to 6.5 Gm. This patient is still active now two and one-half years after the first treatment.

*History.* Mrs. Kathleen B. was admitted to the Mount Sinai Hospital on March 30, 1946, at the age of 47 years, with the diagnosis of multiple myeloma. As far back as September, 1944, she had noticed dull, gnawing pain in the right thigh. In November, 1944, pains in the lower ribs set in which increased in severity, so that in September, 1945, she was obliged to walk with a cane. There was a history of diabetes during the year preceeding admission. In October, 1945, she had been admitted to the Queens General Hospital where x-ray examination showed areas of rarefaction throughout the skull, right femoral head and neck, shafts of both femurs and pelvis. There was also an osteolytic area over the right second rib. She received x-ray treatment to the anterior and posterior part of the right pelvis (1800 r) without relief. Sternal aspiration showed a predominance of plasma cells suggestive of multiple myeloma. Subsequently, a second series of x-ray treatment (3000 r) was given to the right hip through anterior and posterior portals without improvement.

When in March, 1946, she was admitted to the Mount Sinai Hospital she was in a debilitated condition. She could hardly lift her head from the pillow. In order to sit up in bed, she had to roll over and pull herself up into an upright position. This maneuver caused considerable pain. Examination was difficult, but revealed tenderness of the bones, especially the spine, ribs, and right hip. The blood pressure was 138 systolic and 58 diastolic. Hemoglobin was 85 per cent, red blood cells 4,800,000, white blood cells 6,100 with a normal distribution (table I). The urine showed 2 plus Bence-Jones protein and occasionally a trace of glucose. Sternal marrow puncture revealed the typical picture of a plasmocytoma. Biochemical examination of the blood disclosed a blood urea nitrogen of 18 mg. per cent, non-protein nitrogen of 35 mg. per cent, a uric acid content of 4.2 mg. per cent and hyperglycemia (fasting blood sugar, 190 mg. per cent). The albumin (3.9 Gm. per cent) and the globulin (1.9 Gm. per cent) content of the serum were both low normal (table II), and the formol gel reaction of the serum was accordingly negative or occasionally weakly positive. The renal function was very satisfactory. The concentration test went up to 1.026. The phenolsulphonphthalein test showed an excretion of 55 per cent in two hours.

Examination of the skull, long bones, chest and spine again showed numerous destructive lesions throughout the skeleton (figs. 1a, 2a). Most of the lesions were small, but in the right frontal bone, the head, neck and shaft of the right femur, as well as the shaft of the left femur and the upper end of the left radius, the lesions were fairly large. There was an extensive destructive lesion involving the right second rib associated with an extrapleural soft tissue mass. There was no demonstrable involvement of the lungs and no evidence of increased intracranial pressure. In addition to the neoplastic involvement of the spine,

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\* From the Second Medical Service of the Mount Sinai Hospital, New York.

there was evidence of a moderate hypertrophic spondylitis, increased lumbosacral angle and rudimentary cervical ribs.

Stilbamidine treatment was started on April 4, 1946 and after the third injection considerable improvement of the pain was already obtained. During the first series of injections which lasted until May 5, 1946, 2.25 Gm. of stilbamidine were given. The patient could then move around without pain. The large myeloma in the right femoral neck gave rise to great concern because it was felt that walking might well lead to a pathological

TABLE I

*Kathleen B. Case of multiple myeloma treated with stilbamidine*

DATE	HEMOGLOBIN	RED BLOOD CELLS	WHITE BLOOD CELLS	BLOOD PICTURE	TOTAL DOSE OF STILBAMIDINE GIVEN
	<i>per cent</i>	<i>million</i>			
4/ 1/46	85	4.8	6,100	normal	
6/ 5/47	80		6,000	normal	after 2.85 Gm.
11/30/46	80		8,000	normal	after 1.85 Gm.
1/10/47	82	4.55	6,900	normal	
3/24/47	73		8,000	normal	
4/22/47	87		7,500	normal	after 2.85 Gm.
10/ 7/47	11.6 Gm.	3.8	5,850	normal	
8/ 1/48	12.0 Gm.	4.2	9,000	normal	

TABLE II

*Kathleen B. Case of multiple myeloma treated with stilbamidine*

DATE	BLOOD UREA NITROGEN	NON-PROTEIN NITROGEN	URIC ACID	ALBUMIN/GLOBULIN	CALCIUM	PHOSPHORUS	ALK. PHOSPHATASE KING-ARM-STRONG UNITS PER 100 CC.	CEPHALIN FLOCCULATION	TOTAL DOSE STILBAMIDINE GIVEN
	<i>mg. %</i>	<i>mg. %</i>	<i>mg. %</i>	<i>Gm. %</i>	<i>mg. %</i>	<i>mg. %</i>			
4/ 1/46	18	35	7.8	3.9/1.9	11.1	2.5	7	negative	
4/22/46	15		3.7	4.3/3.2				negative	
5/22/46	25		4.3		10.7	2.0	7	negative	2.85 Gm.
5/31/46	23	34	4.8	5.1/1.7				one plus	
6/ 7/46	15		5.3	4.5/1.5	9.2				
11/29/46	13	26	4.9	5.4/1.3	11.0			negative	after 1.8 Gm.
1/ 6/47				6.0/2.5					
3/22/47	18			5.2/1.3					before 2.85 Gm.
10/ 6/47	12			4.9/2.5			16	one plus	
8/ 1/48	17	28	6.7	4.6/3.4	11.5		17	negative	

fracture. It was, therefore, decided to apply x-ray treatment to the neck of the right femur in the hope that this would lead to formation of new bone. At the same time the stilbamidine treatment was continued.

Between May 7 and May 31, 1946, the patient received six radiations to the right hip of 150 r in air. Stilbamidine injections were given twice a week until ultimately the patient received a total of 2.85 grams. She was discharged from the Hospital on June 12, 1946. She then could walk with a limp but without a cane.

On August 26, 1946 she was seen in the Follow-Up Clinic. She felt well. Hemoglobin was 78 per cent, white blood cells 7,200 with normal distribution, sedimentation rate was



5 mm. She then reported that for some time she had been complaining about numbness and a tingling sensation in the face. The paresthesia in the face persisted and on September 16, 1946, clear-cut hypesthesia in the first and second branches of the trigeminal nerve could be found.

During the month of October she had a slight relapse of pain in the vertebral column. She again had glycosuria, which was easily taken care of by daily injections of 15 units of protamine zinc insulin. She then received another series of 12 injections of stilbamidine totalling 1.8 Gm. Shortly after the second course, itching of the nose and face spread to the eyes. There was no response to local medication. Two weeks before the second ad-



FIG. 1a. Skull, April 1946. Multiple osteolytic areas.

mission in November, 1946, the eyes became swollen and red, evidently due to persistent rubbing. Physical examination did not show any abnormal findings. The patient limped around without a cane, but complained bitterly about the paresthesias in the face and in the eyes. The urine again showed strongly positive Bence-Jones reactions. There now was also a considerable amount of sugar in the urine. Hemoglobin and blood picture were normal. The sedimentation rate was 42 mm. per hour. Urea nitrogen (13 mg. per cent); uric acid (4.9 gm. per cent); non-protein nitrogen (26 mg. per cent); calcium (11 mg. per cent); alkaline phosphatase (10 King-Armstrong units); albumin (5.3 Gm. per cent); and globulin (2.1 Gm. per cent) were all within normal limits. Only the blood sugar was high (220 mg. per cent).



In January, 1947, she felt well but the itching of the eyes persisted and she had actual pain in the eyes when she tried to read. There was loss of sensation to light touch and pin-prick over forehead and eyes in the area of the first and second branches of the trigeminal nerve.

She was readmitted on March 21, 1947, because two weeks before admission, after sneezing, pain developed in the upper thoracic spine and persisted. Physical examination was negative except for some tenderness of the spine. There was a pustular eruption over the forehead and mild conjunctivitis, both evidently due to continuous rubbing caused by the paresthesias in the trigeminal area. The physical findings again showed hypesthesia in the first and second branches of the trigeminal nerve. She received 19 injections of stil-



FIG 1b. Skull, August 1948. Osteolytic areas not increased.

bamidine, in total 2.85 Gm. After five injections the pains in the spine were much diminished; after ten injections the pain had practically disappeared. During the latter part of the stilbamidine treatment, the patient received six sessions of spray roentgen-radiation over the entire body. The patient continued to take daily 15 units of protamine zinc insulin. Apart from an increased sedimentation rate (60 mm.), the other biochemical findings of the serum were normal (table II).

In October, 1947, she was very well. In the preceding six months she had gained at least six pounds. She was ambulatory, had no pains at all except when she bent 'way over from the waist. The gait was nearly normal and there was slight kyphosis of the spine. There was still hypesthesia of the first trigeminal branch on the right side and of the first

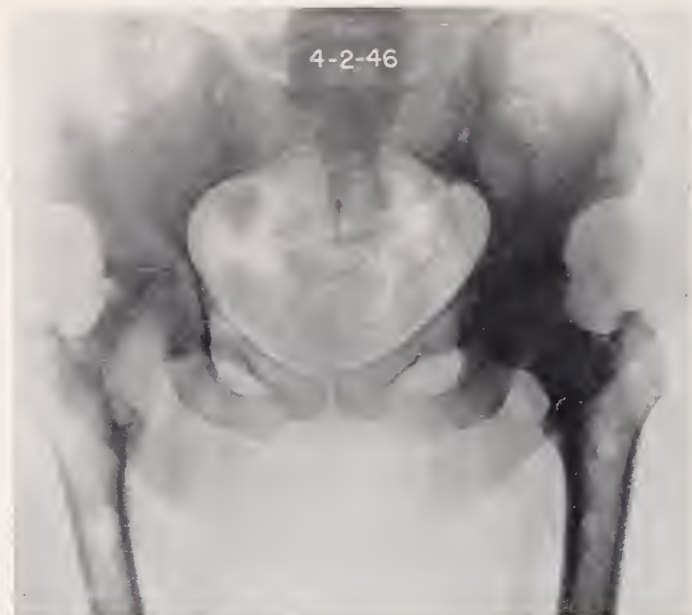


FIG. 2a. Pelvis and upper part of femora, April 1946. Large destructive lesion of neck of right femur and multiple osteolytic lesions in shafts of both femora.



FIG. 2b. Pelvis and upper part of femora, August 1948. No extension of the disease.

and second trigeminal branches at the left side. Bence-Jones protein reactions were still strongly positive.

Since May, 1947, she had not taken any insulin nor did she have a special diet. The trigeminal neuropathy was evidently diminishing in intensity as the itching was considerably less.

In June, 1948, she was seen again. She walked with a limp but did not need a cane, had no pains and felt completely normal. Hemoglobin was 12 Gm. per cent, red blood cells 4,200,000, white blood cells 9,500 with a normal distribution (table I). The blood urea nitrogen was 17 mg. per cent, creatinine 1.4 mg. per cent, calcium 11.5 mg. per cent, alkaline phosphatase 17 King-Armstrong units per 100 cc. (table II). New roentgenograms showed practically the same lesions as in April, 1946, without any marked extension of the osteolytic areas (figs. 1a, 1b, 2a, 2b). Itching of the scalp still persisted.

*Comment.* This patient with multiple myeloma therefore did extremely well in the two-year and three-month interval which elapsed since she first was admitted to the Mount Sinai Hospital. Roentgen treatment given before the first admission to this Hospital had had no influence upon the pains. It seems probable that the three series of stilbamidine treatment she received between April, 1946, and April, 1947, are important factors in the favorable result which was obtained. The roentgen examination performed in June, 1948, indicates that the spread of the multiple myelomas has been halted.

As aforementioned, it seems possible that in this patient the results have been so favorable over a long period of time because she was given much more stilbamidine than the usual dose. In the course of three series she received altogether 6.5 Gm., whereas in other patients with multiple myeloma the maximal dose given hardly ever exceeded 2.5 to 3 Gm. In this patient it was decided not to pay attention to the trigeminal neuropathy caused by the administration of large doses of stilbamidine. She first perceived tingling and numbness of the face about August, 1946. Nevertheless, a second series of stilbamidine injections was given because a slight recurrence of pain in the vertebral column had developed. In March, 1947, a third series was given, notwithstanding the persistence of the trigeminal paresthesia. No wonder that in this patient a very severe form of trigeminal neuropathy developed, which gave rise to particularly disagreeable manifestations, and that it took two years before the signs diminished in intensity.

This experience led to a search for stilbamidine derivatives which have the same favorable influence upon the pains of myeloma patients without the unfavorable sequelae involving the branches of the trigeminal nerve. Such a preparation could be given with impunity in much larger doses and over a much longer period of time than stilbamidine. In this way it might be possible to obtain a more lasting remission of the progress of multiple myeloma than is possible with stilbamidine.

For this purpose, 2-hydroxystilbamidine\*\* was investigated. Other investigators had already reported that this preparation has a strong leishmanicidal

\*\* Kindly provided by May & Baker, thanks to the good offices of Merek & Co., Rahway, New Jersey.

effect and that the toxicity of this preparation for hamsters was no greater than that of stilbamidine (2).

At this time 2-hydroxystilbamidine has been administered to eight patients with multiple myeloma. The preparation was usually dissolved in 10 cc. of water and injected intravenously, every day or every other day. The results, as far as the pains are concerned, were excellent in seven of the eight patients with multiple myeloma. Until now no trigeminal neuropathy has developed, although in three patients more than the customary dosage of stilbamidine (2.5 Gm.) was administered (4.0, 4.2, and 6.2 Gm.). No unfavorable influence upon the kidney function has been evident. In four of the eight patients treated, 2-hydroxystilbamidine led to the formation of basophilic granules in the cytoplasm of the myeloma cells, just as has been described after injection of stilbamidine (3). It was possible to demonstrate that the basophilic granules

TABLE III  
*Effect of 2-hydroxystilbamidine on multiple myeloma*

	TREATMENT								INFLUENCE ON PAINS	TIME OF OBSERVATION	TOTAL DOSAGE	BASOPHILIC GRANULES IN MYELOMA CELLS
	Blood Urea Nitrogen		Non-Protein Nitrogen		Phenolsulphophthalein test		ALBUMIN-GLOBULIN	BENCE JONES PROTEIN				
	Before After		Before After		Before After							
	Mg. %	Mg. %	Mg. %	Mg. %	%	%	Gm. %	months				
J. S.	18	8			75		2.2 8.0	+++	Favorable*	5	2.4	++
S. B.					25		4.3 1.8	++	Favorable	3½	2.2	—
P. C.			42		35	35	2.3 9.5	—	Favorable	2½	6.25	++
P. B.	13	26	57	43	50	50	4.7 2.5	—	No relief		2.8	+++
I. T.	17	21	21	43	65	60	3.3 6.2	—	Favorable	2½	4.0	—
B. S.	14	19	28	34	70		2.2 7.6	—	Favorable	2	4.2	++++
G. A.	16	27	43	39	25	30	2.9 4.4	—	Favorable		2.25	—
R. B.	29	21	36	37	60	65	2.4 6.5	—	Favorable		1.95	—

\* Died 5 months after termination of treatment.

which develop after 2-hydroxystilbamidine treatment also contain considerable amounts of ribose nucleic acid.

Table III reviews the results obtained.

#### SUMMARY

2-hydroxystilbamidine has, like stilbamidine, a favorable influence upon the pains of myeloma patients. In contrast to stilbamidine it seems that 2-hydroxystilbamidine does not lead to a trigeminal neuropathy. 2-hydroxystilbamidine can therefore be given in much larger doses than stilbamidine.

The action of 2-hydroxystilbamidine on myeloma cells seems to be identical to that of stilbamidine, because both preparations give rise to the formation of large basophilic precipitates in the cytoplasm of the myeloma cells. These precipitates consist, at least partly, of ribose nucleic acid.

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# ERGOTAMINE TARTRATE AND THE "TWO-STEP" EXERCISE ELECTROCARDIOGRAM IN FUNCTIONAL CARDIAC DISTURBANCE

ARTHUR M. MASTER, M.D., LEON PORDY, M.D., AND JOSEPH KOLKER, M.D.

The "2-step" exercise electrocardiogram (1) has been of decisive value in obtaining objective evidence of organic heart disease, particularly coronary artery disease, when all other examinations are normal. These include physical examination, teleoroentgenogram and roentgenoscopy of the heart and a control resting electrocardiogram, consisting of unipolar extremity and unipolar precordial leads (positions 1 to 6), as well as the customary limb leads. However, occasionally one meets a difficult situation in which a distinction must be made between a functional cardiac disturbance and organic heart disease. In a very emotionally unstable person, electrocardiographic alterations will appear even in such an objective trial as the "2-step" exercise electrocardiogram or the 10 per cent oxygen test. Hence, in such a situation, any means which will help distinguish between electrocardiographic responses due to functional heart disturbance and those due to organic heart disease is of great importance. In the case to be described, ergotamine tartrate provided the means of such differentiation.

H. S., a woman 38 years old, was first seen in consultation in February, 1948. Her chief complaint was palpitation since the age of 16. For years she had been troubled with attacks of paroxysmal rapid pounding of the heart. The bouts of tachycardia were of short duration, lasting a few seconds to a minute. The onset was sudden, the termination gradual. These spells were sometimes precipitated by worry or emotion, but they came on most frequently without any obvious reason—commonly at night and before the menstrual periods. The patient was intelligent and worked hard as a housewife, taking care of her children and striving to make ends meet. She was in moderate circumstances and very much concerned about her financial situation.

Physical examination disclosed an asthenic, nervous woman. The heart was not enlarged, the rhythm regular and the rate 76 beats per minute. A short systolic murmur was heard at the apex. The heart sounds were strong. The blood pressure was 130 systolic and 80 diastolic. The other features of the examination were not significant.

The teleoroentgenogram disclosed a heart at the lower limits of normal in size. On fluoroscopy, the cardiac contractions were dynamic. The electrocardiogram was entirely normal.

The "2-step" exercise electrocardiogram, taken on February 16, 1948, was abnormal, i.e., after making a standard number of trips (23 in  $1\frac{1}{2}$  min.) there were RS—T depressions in leads V 4 and II. The control resting tracing was normal and return to it occurred 5 minutes after cessation of exercise (fig. 1).

A 10 per cent oxygen test was performed on March 3, 1948 (fig. 1). The patient was very much disturbed by the mask and the test was stopped at the end of 6 minutes instead of the customary 20. Nevertheless, it was already positive, the 6-minute reading disclosing RS—T depressions of 1 mm. in lead II, 2 mm. in V 4, and a negligible amount in leads I and III—a total of more than 3 mm. RS—T depression in the 4 leads.

Clinically, it was our impression that the patient was suffering from a psychoneurotic state. She was deeply concerned about her heart and continuous reassurance was necessary.

Anxiously she would inquire every few moments as to whether she had heart trouble and she would say that she wanted to live since her small children needed her. We persuaded her to allow us to continue our tests so that we could prove to her that her trouble was entirely nervous in character.

Another anoxemia test was attempted on March 15, 1948 (fig. 2). The control resting electrocardiogram was normal (fig. 2A). It was decided to use only one lead, namely V<sub>4</sub> (fig. 2 B, C, and D) for our purposes, since this derivation had displayed the most conspicuous changes following the "2-step" exercise test and during the first anoxemia test. When the mask was applied and connected to room air, even before breathing of 10 per cent oxygen was attempted, the electrocardiogram revealed an RS-T depression of 1 mm. (fig. 2B). This was unquestionably a response to the patient's disturbed state of mind.

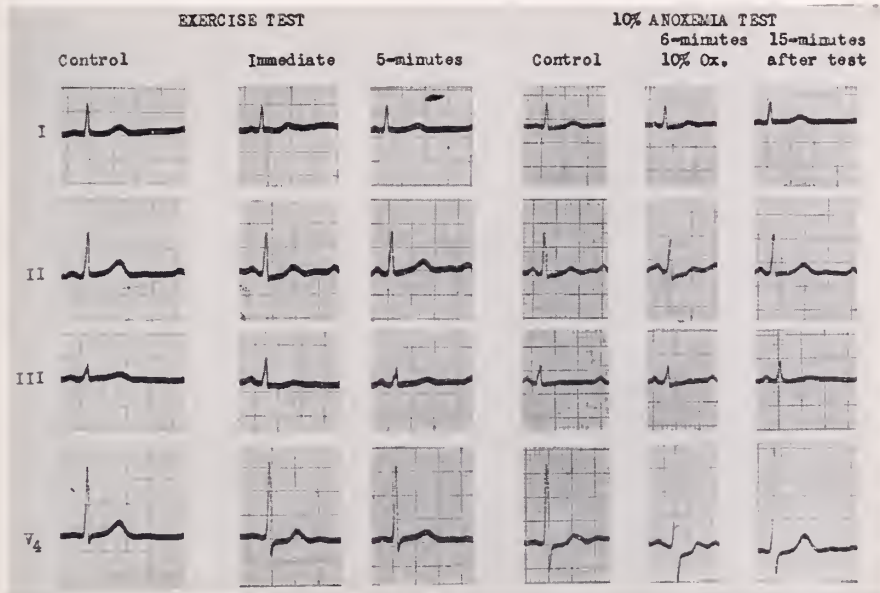


FIG. 1. H. S., a woman of 38, quite neurotic, with a history of attacks suggesting paroxysmal tachycardia. Physical examination entirely negative. Control resting electrocardiogram normal, but after the standard "2-step" exercise the electrocardiogram was definitely abnormal, with RS-T depressions in leads IV and II. Similar, but more conspicuous, changes appeared 6 minutes after breathing 10 per cent oxygen.

The mask was left on and the 100 per cent oxygen tank was started. Nevertheless, the 1 mm. S-T depression persisted for 5 minutes (fig. 2C). The 100 per cent oxygen tank was then turned off, but the mask left on the face so the patient could again breathe room air. As long as the tank was not placed in use the patient was more at ease and the RS-T depressions became shallower in ten minutes. We then again connected the 100 per cent tank to the face mask, but once more the use of a tank disturbed the patient; although she was breathing 100 per cent oxygen, the RS-T depressions deepened to 1 mm.

Without the patient's knowledge the 10 per cent oxygen tank was switched on. A tracing at one minute still revealed an RS-T depression in lead IV (fig. 2D). With reassurance the patient became less panicky and despite 15 minutes of anoxemia, i.e., breathing the 10 per cent oxygen, the tracing returned to normal (fig. 2E: first column of the anoxemia test), whereas the oxygen test on March 3, 1948 had been quite positive. With the movements incident to the removal of the mask at the end of the 20 minutes of anoxemia, the patient

became frightened again and RS—T depression reappeared in lead IV (fig. 2E, second column).

By this time, of course, we were quite convinced that the patient's abnormal electrocardiogram was on the basis of emotional imbalance and not caused by organic cardiac impairment. To demonstrate this we decided to use ergotamine tartrate. Biorck (2) of Sweden

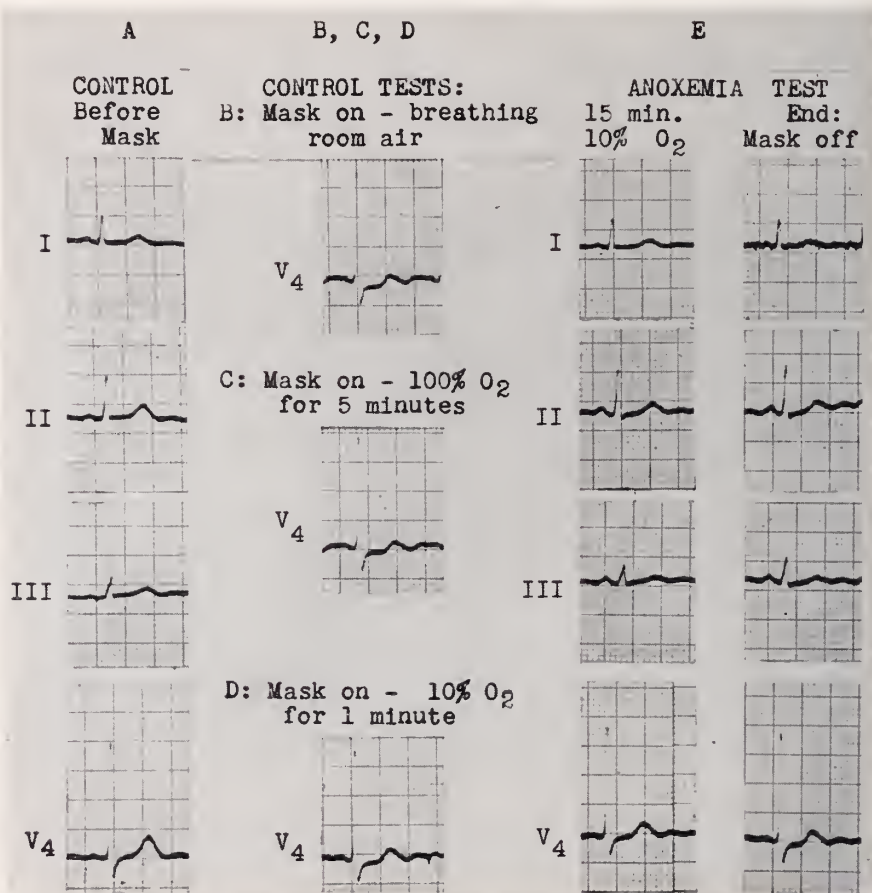


FIG. 2. A. Control electrocardiogram normal. B. On application of mask to face, the patient became nervous, and, although breathing air, the RS-T segment in V4 became depressed, and C. remained depressed even after breathing 100 per cent oxygen for 5 minutes. D. Without the patient's knowledge, the 10 per cent oxygen tank was switched on, and the electrocardiogram was still abnormal in lead V4 after 1 minute. E. With reassurance the patient became less panicky and despite 15 minutes of anoxemia, i.e., breathing the 10 per cent oxygen, the tracing reverted to normal. With movements incident to mask removal at the end of the test (20 minutes), the patient became frightened again and RS-T depression reappeared in V4.

had given this drug intravenously to his emotionally unstable patients, before using the anoxemia test. He had concluded that one could differentiate between the electrocardiographic changes in those with organic heart disease and in those with functional heart disturbance by using ergotamine during the anoxemia test. The rationale was that this drug, as a sympatholytic agent, abolished the effects of the patient's fears conveyed to the heart by the sympathetic nervous system. It did, in fact, prevent the appearance of deviations



from the normal in the electrocardiogram in his anoxemia tests. We decided to use the same technique for the standard "2-step" exercise test. If there were no underlying heart disease, but rather sympathetic overstimulation, ergotamine would prevent the appearance of RS-T depressions in the electrocardiogram. This is exactly what took place.

The "2-step" exercise electrocardiogram was definitely positive on May 13, 1948 before ergotamine was given. RS-T depressions appeared in V 4, II and III after the standard "2-step" exertion, that is, 23 trips in 1½ minutes (fig. 3). Ergotamine tartrate, 0.5 mg., was administered intravenously about an hour and a half after cessation of the foregoing "2-step" test. Thirty-five minutes after the injection, the "2-step" exercise was repeated, and for the first time the electrocardiogram following this standard exercise was normal (fig. 3). This result was obtained in spite of the fact that the patient was quite upset because of nausea and vomiting following the ergotamine.

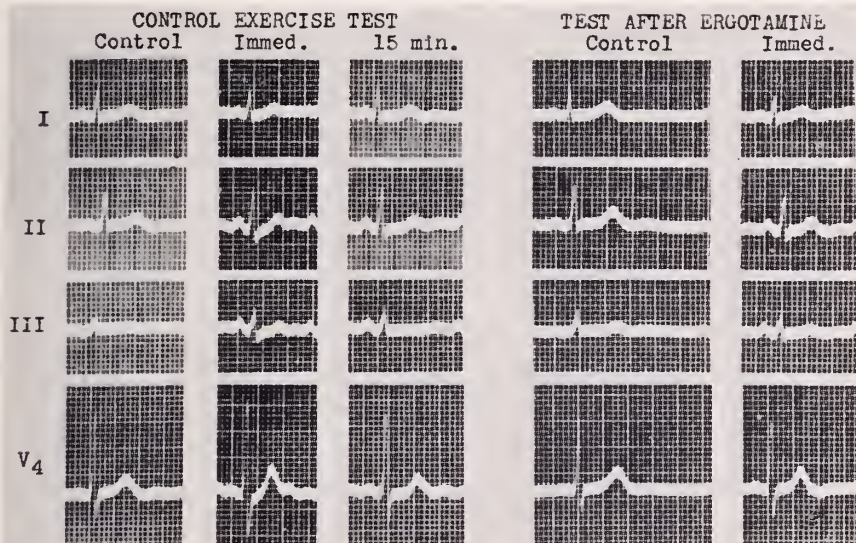


FIG. 3. Control electrocardiogram negative, but immediately after standard "2-step" exercise, RS-T depressions in V 4 and leads II and III. Ergotamine tartrate, 0.5 mg., injected intravenously about 1½ hours later. In 35 minutes the "2-step" exercise was repeated, but no changes in the electrocardiogram occurred.

Thus it would appear that in our patient the changes in the electrocardiogram which were disclosed after the "2-step" exercise test and during the anoxemia test, or simply when the patient was apprehensive, were on the basis of sympathetic nerve overactivity and not due to organic coronary disease. Further evidence supporting our conclusion was obtained by the changes in the electrocardiogram when the patient stood up; a negative tracing altered to abnormal: T 1 and 4 became smaller, T 2 and 3 became isoelectric (flat) and minimal RS-T depressions appeared. However, when this "positional" maneuver was tried 20 minutes after the injection of ergotamine, the electrocardiogram remained normal. Wendkos (3, 4) has already used this method to demonstrate sympathetic nerve impulse overactivity.

*Comment.* The patient was a woman, aged 38 years, showing pronounced psychoneurotic features and suffering from episodes of what appeared to be paroxysmal tachycardia. Ergotamine tartrate, a sympatholytic drug, was used

to demonstrate that changes in the "2-step" exercise electrocardiogram were due to over-stimulation of the sympathetic nervous system and not caused by coronary artery disease.

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THE GREATER MOUNT SINAI HOSPITAL UNDER WAY

The Board of Trustees announced on September 1st that Dr. Martin R. Steinberg, who had been Associate Director of the Hospital, would succeed Dr. Joseph Turner as Director. According to the announced plan, Dr. Turner's new title would be Consultant to the Board of Trustees and his new function would deal with the new building program.

The President of the Board of Trustees in making his announcement concerning the planned buildings merely stated that they would be three in number: a Maternity Pavilion and two laboratory structures, and that they would serve as the beginning of the Greater Mount Sinai Development plan. The latter was under consideration during the past decade; the details were vague and were characterized by a shifting of accents. Now, however, the plan has assumed a much more definite pattern, and Dr. Steinberg was good enough to give a brief outline of its three major divisions.

THE FIRST DIVISION—THE 'BRICK AND MORTAR PLAN'

The excavation which is already in progress will extend from the south building line of the Private Pavilion, on the north, to the north building line of the Nurses' Home between 98th and 99th Streets, on the south, and from Fifth Avenue, on the west, to Madison Avenue, on the east. It will provide room for three buildings.

*The Maternity pavilion.* This building will be erected on Fifth Avenue abutting against the south wall of the Private Pavilion. Because of this abutment any of the floors in the Private Pavilion can be extended into the new building and, as a matter of fact, two floors of the new building will be extensions of the Private Pavilion.

In addition to the beds on these two floors, it is planned to provide 107 obstetric beds, the private, semi-private and ward beds being approximately equal in number. One floor will be devoted to facilities for the treatment of premature infants and the ground floor to an out-patient department for obstetrics. While the specifications have not yet been completed, many innovations and every proven new facility will be included.

*The Laboratory building.* On the Madison Avenue front of the plot, the plans call for a structure which will house chemistry, bacteriology and research laboratories. The present Lewisohn Laboratory Building will be renovated and given over exclusively to the Department of Pathology.

*The Berg Institute of Research.* Between the two buildings, a 4 story structure to be known as the Berg Institute of Research will be erected to house several research departments.

The bed of 99th Street between Fifth Avenue and Madison Avenue was given to the Hospital by the city and will be used as part of the Hospital grounds. Access to the Berg Building will be through an archway on Fifth Avenue between the Private Pavilion and the Maternity Pavilion.

*Kitchen and food centre.* Under the group of buildings, a new centralized kitchen and staff dining rooms will be constructed. The dining rooms will be air conditioned and will be large enough to accommodate the entire staff except student and staff nurses who will continue to use their present facility in the Nurses' Home. In the new kitchen a large dietary staff will prepare all food served in the Hospital except a part of the menu for Private Pavilion patients which will continue to be provided from the Private Pavilion kitchen.

*Parking lot.* A parking lot is already being constructed. It will extend along the east side of Madison Avenue and will have openings on 100th and 101st Streets. Room is provided for 50 to 55 cars; it will be attended throughout the 24 hour period.

*Transition period.* The Maternity Pavilion on its completion will house all private patients for a limited time until a major renovation program is carried out in the present Private Pavilion.

*Further extension.* Present planning also calls for the replacement of the ward, administration, Out-Patient Department and utility buildings with a new group which will occupy the block between 100th and 101st Streets and part of the block between 100th and 99th Streets.

A Psychiatric Pavilion may be situated within the present Hospital boundaries or perhaps directly adjacent to it.

#### THE SECOND DIVISION

This has to do with a reorientation of the approach to the patient. The aim is to dignify the ward and the out-patient department patient as well as the Private and Semi-private patient by giving as much thought and attention to his sensitivity and his ego as we do now to his ailments. Stated as it is here in one sentence, it seems a simple task and hardly of the magnitude which should rank with as complex an undertaking as the construction of buildings. Actually, it entails a carefully planned, complex educational campaign. The entire staff will have to learn new values and new etiquettes. In the end, if we are successful, we shall have learned to do much more for the patient than healing his organic lesions and in the process, we should make our Hospital work more effective and our interrelationships happier.

#### THE THIRD DIVISION

In this phase of planning, the future role of the voluntary hospital is considered. The plan is predicated on the basis that the hospital of the near future will be semi-private in character, with most of its patients being financed by hospital insurance. The hospital will become the health center. Many physicians will locate their private offices within the hospital, and center all their activities there. Group practice is becoming a lusty infant and needs to be reckoned with in planning. The rapid growth of the laboratory and investigative medicine makes necessary additional space and specialized equipment. The intensification of specialization which followed the rapid increase in the whole body of scientific knowledge points up the necessity for expanded educational programs which bid fair to make the larger hospital a post-graduate school.

Finally, the development of the concept of the role of the hospital in the maintenance of health with an extension of its facilities into the home of the patient is receiving a share of the planning effort.

As the program develops and space in this journal is made available, a fuller description of each division of the plan will be given.

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Histochemical Distribution of Alkaline Phosphatase in Dog Liver after Experimental Biliary Obstruction.* M. WACHSTEIN AND F. G. ZAK. Proc. Soc. Exper. Biol. & Med., 62: 73, May, 1946.

Bile capillaries show distinct phosphatase activity in the normal dog liver. This property can be used for their microscopic demonstration. After ligation of the common bile duct there is not only marked dilatation of the bile capillaries but also apposition of phosphatase around them which increases with the duration of the experiment. The changes in the distribution of alkaline phosphatase in histochemical preparations favor the assumption that the increase of serum phosphatase in liver damage is due to the inability of the liver cells to excrete the enzyme rather than the increased production in the liver itself.

*Bismuth Pigmentation; Its Histochemical Identification.* M. WACHSTEIN AND F. G. ZAK. Am. J. Path., 22: 603, May, 1946.

Castel's method for the demonstration of bismuth in tissue preparations was adapted for the identification of bismuth sulfide in frozen sections, paraffin sections, and in gross specimens. The method permits histochemical identification of bismuth sulfide pigmentation in any tissue. Bismuth discoloration of the colon is apparently not infrequent. It was found in 4 of 340 consecutive autopsies. Even small amounts of injected bismuth may lead to the deposition of histochemically demonstrable bismuth sulfide in the large bowel. The inclusion bodies found in the renal epithelial cells following the use of bismuth preparations frequently give a positive reaction with Castel's reagent.

*Relation of Tobacco Smoking to Arteriosclerosis Obliterans in Diabetes Mellitus.* L. A. WEINROTH AND J. HERZSTEIN. J.A.M.A., 131: 205, May, 1946.

The peripheral circulation of 301 male diabetic patients was studied in the Metabolism Clinic and the wards of the Mount Sinai Hospital. The purpose of the study was to determine whether or not there was any relationship between tobacco smoking and the presence of arteriosclerosis obliterans. All patients were questioned about the presence or absence of intermittent claudication. The patency of the femoral, popliteal, anterior tibial, dorsalis pedis and posterior tibial arteries was determined. About two thirds of the patients had oscillometric studies. It was found that among the 83 non-smokers 37.3 per cent had arteriosclerosis obliterans and that of the 218 smokers 57.8 per cent had the disease. In the younger age groups the difference was even more striking. Thus in the decade from 50-59 years 22.2 per cent of the non-smokers and 56.6 per cent of the smokers had the disease. The incidence of occluded blood vessels was greater among smokers regardless of the severity of diabetes, of adequacy of control, presence of obesity or hypertension.

*Psychogenic Factors in Oral Disease.* R. S. GILBERT. Oral Hygiene, 36: 998, June, 1946.

There is probably a considerable psychogenic component in the etiology of oral and dental disease. The mouth is a region surcharged with enormous psychological potential. Affective states interacting on the hormonal and vegetative nervous systems may modify the chemical and physical composition of the saliva and thus provide a favorable milieu for the processes of dental decay. Prolonged periods of emotional tension which lead to

changes in the vascular tonus of the oral tissues may be a significant factor in the causation of paradentosis. Some mouth lesions suggest a psychogenic origin. Herpes simplex and labialis regularly occur in many individuals after an emotional upset. Instances of patients who developed lichen planus after a severe psychic trauma have been reported.

*Inhibitory Effect of Thiamine on the Vasoconstrictor Action of Nicotine Tested in the Lacwen-Trendelenburg Preparation.* H. HALMOVICI AND E. P. PICK. *Proc. Soc. Exper. Biol. & Med.*, 62: 234, June, 1946.

Thiamine, in very small concentrations (1:10000), inhibits the vasoconstrictor action of nicotine in the frog vessels. The inhibiting action of thiamine is linked with the thiazole moiety of the molecule, the pyrimidine group being ineffective. Thiouracil, nicotinamide, para-aminobenzoic acid do not inhibit the action of nicotine; sulfathiazole has an inhibiting effect only in a relatively high concentration (4:1000). The site of action of thiamine seems to be at the myoneural junction in the striated muscles and at the postganglionic nerve endings or in the muscle elements of the vessel walls in the smooth muscles.

*The Consistency, Opacity, and Columnar Cell Content of Gastric Mucus Secreted under the Influence of Several Mild Irritants.* F. HOLLANDER, J. STEIN AND F. U. LAUBER. *Gastroenterol.*, 6: 576, June, 1946.

A study was made of the relative frequency of occurrence of various characteristics of acid-free gastric mucus, collected from dogs' Heidenhain pouches under the influence of various stimuli. About 500 specimens were examined. The results are summarized as follows: 1. Mucus may be fluid or jelly-like or of any intermediate consistency, irrespective of stimulus. 2. It may be transparent, completely opaque, or translucent. 3. The secretion may contain (a) neither cells, cell residues, nor even detritus; (b) much detritus, but no intact cells; or (c) large numbers of columnar cells—singly, in ranks, and in clumps. Erythrocytes may also be present occasionally; leucocytes occur more commonly. 4. Increasing viscosity, opacity, and columnar cell content are correlated statistically with each other and with the irritating power of the stimulus. 5. From these observations it may be inferred that pure mucus is (a) colorless, (b) transparent, (c) of variable consistency, and (d) free of suspended material. Opacity of a specimen as collected is the result of suspended material, chiefly desquamated columnar cells. 6. Two alternative hypotheses are offered to explain the variations in viscosity of the mucus. First, neck chief cells and columnar cells are distinct exocrine glands, giving rise to mucoid and mucus secretions respectively. Second, neck chief cells are precursors of columnar cells, and mucus—irrespective of its viscosity—may be elaborated by both of them. The chief function of mucus secretion in the digestive tract is to protect the underlying glandular epithelium against various forms of irritation. This entails two processes, which probably are independent: exocrine secretion *per se* and desquamation of the surface epithelium. Since exfoliation affords auxiliary protection, the concept of a gastric "mucus barrier" has been redefined to include both of these processes.

*The Effect of Alcohol on the Personality Inventory.* H. A. ABRAMSON. *Ann. New York Acad. Sc.*, 46: 535, July, 1946.

The Minnesota Inventory provides a suitable clinical technique for obtaining fairly constant personality profiles, over extended periods, in an objective fashion. As such, it is an excellent method for rapidly obtaining a psychosomatic history. It appears from limited studies that repetition of the test (without alcohol) may reflect a change in attitude, more by the variation in the height than by the shape of the curve. For this reason, it is believed that, even when within normal limits, the shape of the curve may indicate the trend of future difficulties under adverse emotional stress. Following the consumption of sufficient alcohol to produce moderate intoxication, the basic attitudes of the individual remain essentially unchanged in the special group of moderate drinkers studied here. Even though the personality profile remains essentially unchanged, the consistent responses after



alcohol represent only a part of the items chosen for scoring. Other items are added, or omitted, after alcohol; usually without a marked change in the shape of the curve and with only minor changes in the values of certain categories. This indicates that there is an inherent validity, both in the group of questions comprising the test, and in the method of its administration. Further evidence of the presence of an inherent validity of the test lies in the analysis of the "*Consistency Profiles*." The consistency profiles are profiles constructed from the items answered in the same way before, and after, alcohol. The shape of the consistency profiles is similar to the profile obtained while sober or after alcohol, although fluctuations in special categories occur. It would appear that studies of the effects of alcohol ingestion may be readily extended to different levels of intoxication and to different groups, especially alcoholics, in an objective fashion. An analysis of the special items answered differently before, and after, alcohol is planned. Investigations of fluctuations of this type may lead to new and simplified technics for more rapid resolution of unconscious conflicts.

*Acute Aseptic Meningitis Following Paravertebral Lumbar Sympathetic Blocks.* M. H. ADELMAN AND C. I. IRWIN. *Anesthesiology*, 7: 422, July, 1946.

In a series of 165 cases, 2 patients, given lumbar sympathetic nerve injections with procaine, developed a clinical picture of acute meningitis within six to nine hours after the nerve blocks. The clinical course was comparatively benign and of seventy-two hours' duration; no untoward sequelae resulted. Studies of the cerebrospinal fluid failed to reveal any responsible bacteria. The sequence of events in the clinical pictures, the repeatedly negative bacteriological studies and the normal cerebrospinal sugar titers pointed to a non-infectious causative agent.

*The Future of Medical Practice.* G. BAEHR. (Commencement address delivered to the graduating class of the Long Island College of Medicine, New York, March 28, 1946.) *Alumni Bull. Long Island College Med.*, 2: 3, July, 1946.

The broader aspects of medicine as a social science are stressed, as well as the constantly changing values in its progress. In a consideration of the physician in the world of tomorrow, the need for both group practice and the organization of some form of prepayment for medical care, is envisioned. A gradual obsolescence of the present methods of medical practice is deemed inevitable. Group practice units are contrasted with the Mayo and Lahey clinics, which latter have no true social significance nor do they include the general practitioner as an integral part of the organization. The physician-patient relationship need not be sacrificed in group practice and the general practitioner will have a better opportunity to keep abreast of medical progress. The advantages of group medical practice include increased remuneration to the average individual physician and an opportunity for the practice of true preventive medicine, as it is obviously to the advantage of the group to prevent as much illness as possible. It also offers the physician a richer professional life, periods of vacation and study, a predictable income and retirement benefits. Most medical schools remain aloof from the responsibilities of the Changing Order. Prepayment plans are seriously endangered by the insistence of some local medical societies on a fee for each service with consequent multiplication of services, and restriction to benefits solely to persons earning less than \$2500. Both restrictions will, it is felt, make the sale of the plans almost impossible, as proven by the experience of several comprehensive medical programs. Unless these restrictions are lifted the widely supported Health Insurance Plan of Greater New York will never be effective, and thus shortsighted leaders of medical societies are playing into the hands of the advocates of national compulsory health insurance. The deceptively simple Wagner-Murray-Dingell bill by no means answers the medical problem, fails to improve the standards of medical practice, and creates the irresistible temptation of physicians to increase their income by needless multiplication of medical services. The extremes in the medical standards of several states, as well as the marked contrasts between rural and urban practice require adequate equalization before



any nation-wide system can be expected to work. After three years of study the Committee on Medicine and the Changing Order of the New York Academy of Medicine has presented alternative proposals which include limited grants-in-aid to each of the various states which will adopt a medical care program for its people that will meet acceptable standards, with proportionately larger grants for states with low per capita incomes. Each state will thus be in a better position to determine the manner of medical care, which may well include voluntary medical insurance. It is felt that an evolutionary transformation of medical practice rather than the immediate adoption of a national system of compulsory medical insurance will ultimately offer more in the nature of therapeutic and, especially, preventive care. Whether by one method or another, the ultimate prepayment of the costs of medical care is inevitable and can only lead to improved standards and greater economic security.

*Influence of Experimental Kidney Damage on Histochemically Demonstrable Lipase Activity in the Rat.* M. WACHSTEIN. J. Exper. Med., 84: 25, July, 1946.

Lipase activity was found in the cytoplasm of the proximal convoluted tubules in tissue sections of rat, rabbit, dog, mouse, hamster, and guinea pig, stained according to Gomori's method. Uranium and mercury poisoning do not inactivate the enzyme in necrotic cells of the proximal convoluted tubules. Its activity diminished in the atrophic and regenerating cells of the kidneys of rats, surviving the acute phase of the intoxication. In the acute stage of choline deficiency marked reduction in enzymatic activity was seen in the necrotic tubules, and in the atrophied and regenerating tubules in the subacute 10 to 12 days after ligation of the ureter. In sections stained for alkaline phosphatase activity nearly identical alterations were found. Experimental damage influences both histochemically demonstrable enzymes in a similar manner.





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## THE EDWARD GAMALIEL JANEWAY LECTURE

THE STRUCTURE OF THE METABOLIC PROCESS IN THE NEPHRON<sup>1</sup>

JEAN OLIVER, M.D.

*(Brooklyn, N. Y.)*

I think a pathologist can feel a very special sort of gratification for the honor of your invitation to deliver a Janeway Lecture, for if the eminence of achievement of those who have preceded him in this series is a cause to him for a self-searching and critical examination of his own position, he can at least take heart in the recollection that Doctor Janeway, truly a heroic figure in the medicine of his time, was (one might say by avocation) a Professor of Pathology and President of the New York Pathological Society.

It was true in those days that pathology led and directed medicine by the strength of its morphological discipline. Today those who were responsible in the past for the pioneering of the advance, and who still might be expected to lay its groundwork of structural knowledge, have been overrun and outdistanced by the dynamic surge of the functionalists and biochemists. So far behind do the erstwhile pioneering pathologists lag that the most elementary knowledge of tactics suggests that the front lines of medicine, if far advanced, are certainly not consolidated. And there is danger in such a position.

Now the correction of such a situation is surely not for the pioneers to drop their picks and shovels and climb aboard the pursuit planes for what would doubtless be a personally thrilling, but surely a tactically futile, joyride. The task still remains of building the solid framework of the structural line that will support an even greater advance. This was the pathologist's job in the time of Janeway and there is no one else to do it now.

What I shall show tonight is a preview of such an effort.<sup>2</sup> For some time at Long Island College of Medicine we have been trying to furnish a tentative framework of structural form for the elaborate and detailed functional knowledge that now exists of the metabolic process in the nephron. There is nothing of any great novelty in our method: its most fundamental procedure, microdissection, might be described as primitive. Fats, minerals, and carbohydrates can be identified by various means and seen either directly or indirectly in the renal

<sup>1</sup> From the Department of Pathology, Long Island College of Medicine, Brooklyn, N. Y.

Presented at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on April 13, 1948.

<sup>2</sup> This work was carried on from 1944 to 1946 under an OSRD contract, in cooperation with Doctor Thomas Addis, as an investigation of the effect of proposed blood substitutes on renal structure and function. It is being continued by a group supported by the Life Insurance Medical Research Fund and the Commonwealth Fund, consisting of the writer and his associate investigator, Muriel MacDowell; Doctor Werner Straus, biochemist; and Frances Mottram and Lucretia Allen, assistants.

tissues under varying functional states (1). The problem, therefore, becomes a matter of the localization of the functional process or change in some structural element such as the nephron, the tubule cells, or in cellular constituents, such as rodlets, droplets, mitochondria or microsomes. Tonight I shall limit myself to certain aspects of the structural changes that are associated with the handling of proteins.

That the ultrafiltrate of the glomerulus is less commonly free of protein than the idealism of the physiologist leads him to believe is becoming more commonly the belief of clinicians and pathologists who follow the ups and downs of the daily adjustment of the organism to its environment. The bladder urine is, however, free of any considerable amount of protein under "normal" circumstances, and this fact, in the light of our knowledge that it has been a hundred times concentrated during its passage through the nephron by the absorption of water, is almost proof in itself that protein also must have been absorbed. That it is indeed absorbed under certain conditions and that it can even be seen in droplet form in the renal cells has been established by Gerard and Cordier (2) and by Smetana (3).

In our study we have made use of the rat as a subject for the investigation of the problem, for the glomerular filter of this animal is relatively more permeable than that of other species to proteins of various source, constitution and molecular size.<sup>3</sup> Most of my descriptions will be concerned with the manner in which the nephron handles native egg white, a mixture of proteins and other substances the molecular size of which is small enough to pass the filter barrier easily. Five hundred to 1000 mg. of diluted egg white were injected into the peritoneal cavity of the rat and 18 hours later, somewhat after the peak of its elimination in the urine, the kidneys were examined by various histologic methods.

Since our purpose is visualization of the finer cytological elements of the tubule cells, the method of Zenker fixation and staining with iron hematoxylin was used for a preliminary survey of the structural changes. By this means the cell organs peculiar to the renal epithelium—the batonnets or rodlets of Heidenhain—are well shown, and with these we will be particularly concerned, for a vast amount of previous investigation has strongly suggested, if not proven, that they are concerned in the functional activity of the renal cell. In Figure 1, cross sections of proximal convolutions of an animal which had received an intraperitoneal injection of 0.9 per cent NaCl and no egg white shows the appearance of these rodlets when the nephron is functioning in a normal manner. They form a closely packed, almost solid, palisade and though a few scattered "granules" or small droplets may be seen, these are in most instances sections of the slender filamentous structures. The contrast with the appearance of sections of the proximal tubule of animals excreting large amounts of egg white is striking (fig.

<sup>3</sup> The proteins examined include gelatin (various preparations), casein, lactalbumen, Bence-Jones body, egg white, crystalline ovalbumen, ovomucoid, hemoglobin (various preparations and sources), globin (human), serum albumen (rat, bovine, human), crystalline bovine serum albumen, serum "globulin" (human), Cohn plasma protein fractions, blood serum (rat, horse, human), various dyed serum proteins.

2). The tubule cells are filled almost to bursting with black-stained, round droplet masses which may be as large as the cell nucleus.

I shall not attempt to describe the appearances observed after the injection of the other proteins except to state that all showed similar changes. The number and size of droplets decreased with increasing molecular size of the injected material. The distinctive appearance of some of them (hemoglobin and the various dye-protein compounds) leaves no question that the droplets contain the injected material.

A casual study of such preparations will show that all cross sections of the renal tubules do not contain the droplets and that there is a great variation in the number present in those in which they are seen. Our first problem of the localization of the metabolic process thus arises. This can be answered clearly and objectively by dissecting a complete nephron from a suitable kidney, placing it on a slide and staining and differentiating with the same method that was used on the section.

In Figure 3 is shown a camera lucida drawing, along with microphotographs of various portions of the nephron, of such a specimen from the kidney of a rat with heavy albuminuria due to a  $\frac{3}{4}$  nephrectomy. The distribution of the droplets is seen to be limited to the proximal convolution and it is further evident that a zone of maximum intensity occurs in the middle of this portion of the nephron. The same localization was found for the egg white droplets, as will be illustrated later, and no great differences were noted with other proteins.

With this first and relatively gross localization of the process of absorption accomplished, we can pass now to a consideration of the structural changes which accompany the passage of the egg white into the cell. In doing this we shall develop our exposition by what might be considered a historical or chronological method, first because it is a logically effective procedure but also because I believe it will emphasize the advantage of assembling the simple data before considering the complex. So many of my younger confreres yearn only to emulate Caspersen and scorn the simple and easily available techniques of Heidenhain.

*Observations by the Classical Methods of Cytology.* Referring again to Figure 2, where rods and droplets in the proximal convolution are stained with iron hematoxylin, one notices that these two elements, the one a cell organ and the other a structure that has arisen in the cell during the absorption of the egg white, are not indiscriminately scattered through the epithelial lining of the tubule. There is a definite pattern which might be described as constituting an inverse ratio of droplets and rods. Where the rods are unchanged from the appearance seen in the non-protein absorbing tubule there are few if any droplets; where droplets predominate, the rods are not simply displaced but are less frequent or have even disappeared. The details of the changes are more exactly shown in Figures 4 to 6.

In Figure 4 is shown the intact palisade of the slender, evenly contoured rodlets in the upper part of a proximal convolution of a nephron which was excreting egg white. As you have seen in Figure 3, there may be no absorption droplets in this

portion of the convolution. In Figures 5 and 6 is shown the appearance in the middle portion of the same nephron, where droplets and rods indicate the site of absorption of the egg white. The rods, swollen and apparently dissolving, are surrounded by a cloud of diffuse material that reacts similarly to the stain and in which can be seen areas of condensation (fig. 5) or definitely round droplets (fig. 6). Again, in passing, I may state that similar changes were seen with all other proteins except gelatins and globin, special cases with which we need not be concerned at this time.

If the obvious implications of such an old fashioned, morphologically interpretive description seem naive, let us accept them for the time, for we shall return to the question of the relation of drops to rods as it becomes increasingly apparent that this relation is the fundamental clue to the solution of our problem.

A change from filaments to drops or granules is, of course, an old story in the cytology of functioning gland cells, and many descriptions of such alterations are recorded for the renal epithelium. Unfortunately, however, the investigators' knowledge in the past of the functional state of the mammalian tubule has seldom been adequate for anything more than the correlation of two uncertain guesses, one structural, the other functional, and such correlations are admittedly difficult to achieve. Accordingly, the literature is filled with descriptions of the transformation of rods to granules or vacuoles or droplets as the structural aspect of such functional states as the tubular excretion of water or salt, for which no actual evidence exists.

Besides its firmer base of inherent functional knowledge, our answer to the problem of correlation becomes more impressive when we show that there are qualitative as well as structural differences in the rods and droplets. After Zenker fixation and the alcohol treatment of paraffin embedding, the rodlets do not retain the methyl violet of the Gram stain. Figure 7 shows cross sections of the proximal convolution of a rat which had received no egg white. The rods are invisible. In Figure 8 it is seen that the droplets in the tubule cells of a nephron absorbing egg white are strongly Gram-positive and so, I may add, are the droplets of all the other proteins examined.

The Gram-positivity of the protein droplets makes available a clearer demonstration of the distribution of these structures in the proximal convolution than is possible with iron hematoxylin, which also stains the rodlets. Figure 11 shows the concentration of droplets of egg white increasing to a maximum as one departs from the glomerulus and then subsequently falling rapidly.

It must be kept in mind at this point—and we shall return to the matter later—that, like all staining reactions, the Gram method depends on the preliminary treatment of the stained material. Under the conditions of the histological preparations described above the rods are negative and the droplets positive. Egg white, spattered in droplet formation on a glass slide and treated with Zenkers and alcohol, as was the embedded tissue, is also Gram-negative. What then is the source of the Gram-positivity of the droplets of absorbed egg white seen in the sections?

The meaning of the Gram stain has long been a problem for bacteriologists and



a recent suggestion of Bartholomew and Umbreit (4), based on the removal of the Gram-positivity of organisms by the action of crystalline ribonuclease, is that it is due to a certain content of ribonucleic acid. Similarly, cytologists, most recently Opie and Lavin (5), have used this enzyme to demonstrate ribonucleic acid in the cytoplasm of cells. The experiment succeeds strikingly with the absorption droplets. In Figure 15 are shown three sections from the same kidney of a rat whose proximal convolutions were filled with droplets. Section A was incubated for three hours at 53° in a veronal buffer at pH 6.8; section B was similarly treated except that the buffer contained 1 mg. of crystalline ribonuclease per cc. Both were then stained together in the same Coplin jar with the Gram method. It is apparent that the treatment with ribonuclease has reduced or completely removed the Gram staining element from the droplets; the droplets, however, have not disintegrated but retain their definite contours as discrete objects, many of them still outlined by a thin coating of methyl violet.

The specificity of action of the ribonuclease has been challenged and statements appear in the literature that even the crystalline preparation has a proteolytic action, due either to contamination or to a lack of absolute specificity in the enzyme itself (6).

The evidence on this point, derived from its action on histological sections, obviously cannot be conclusive, but it is noteworthy that the enzyme in our experiments did not disturb the shape and size of the droplets, as do proteolytic pancreatin preparations. Furthermore, since our droplets are definite, isolated bodies and not a basophilic material distributed diffusely through the cytoplasm of cells (5), it is possible to carry the experiment a step farther, as did Bartholomew and Umbreit, and "plate" the still intact droplets with magnesium ribonucleate. In Figure 15C is shown a contiguous section of the same block that was treated with ribonuclease, along with the one shown in B. It was then washed in water and placed for 12 hours at 37° in 0.5 per cent solution of magnesium ribonucleate, again washed thoroughly and stained with the Gram method. It is evident that the droplets are as strongly Gram-positive as they were before the action of the ribonuclease. Evidently what was taken out can be returned, and with its return Gram-positivity is restored.

If one accepts the specificity of the action of the crystalline enzyme—and the "replating" of the droplets would seem to obviate criticism—then the conclusion that the droplets contain ribonucleic acid in some form suggests strongly that they possess an admixture of some cytoplasmic element. The source of this cytoplasmic constituent may be left for later consideration.

At this point, and in respect to an old tradition, a digression from our description of the cellular changes seems warranted. Since Virchow's time pathologists have maintained the existence of what they designate as "degenerative" processes, which are looked upon, to quote a modern authority, as "the fingerprints of disease." Even if this picturesque figure brings no very exact image to the mind's eye, it at least serves to illustrate our lack of exact comprehension of what a degenerative process is. In any case, the structural picture connected with one aspect of degeneration in the renal epithelium is the presence of fine protein



granules, which are most likely minute droplets, and larger "hyaline droplets" of the same material. The latter are presumed to be of much graver significance than the former and have served the pathologist well for years in those times of stress at clinical-pathological conferences when, in a case of "nephrosis," an epithelial "degeneration" was needed for correlation with clinical evidence of tubule damage.

Recently, the investigations of Gerard, Smetana and others have indicated that the droplets are most certainly not a transformation of the cytoplasm of the cell, but that they are concerned in some way with the absorption of protein. The question still is raised as to whether such appearances are "normal" or whether they are evidence of the improper behavior of "damaged" cells. And a recollection of the ill repute of the "foreign proteins," which we are using so casually in our experiments, may have raised some such qualms.

As to what "normal" means, there seems to be some question: I shall only say in passing that the recent definition of a fellow investigator (7) of the functional aspect of renal activity, has seemed for years to one who is concerned with the structural view of the same disturbances to be the only rational attitude in this metaphysical problem. Certainly from the statistical viewpoint the presence of large droplets of protein in renal cells is not usual or "normal."

The somewhat more practical question of "damage," in the sense that cell activity has been lessened or perverted, and that this is in some way associated with the droplet accumulation, still remains, however. This can be at least indirectly answered. The injection of .00075 Gm. of uranium acetate, as Susuki showed, will damage and even kill some of the cells of the middle portion of the proximal convolution, leaving those above and below this mid-zone structurally unchanged. Three days after such an injection 1000 mg. of egg white were injected as in the previous experiment and 18 hours later the animal killed. In Figure 12 are seen cross sections of the upper, structurally undamaged, portion of a nephron; the well preserved epithelial cells are filled with droplets. Figure 13 shows cells damaged in varying degree; they are filled with irregular accumulations of cellular debris from the disintegration of the rodlets, but there are none of the droplets which filled the undamaged cells.

Droplet formation, then, has occurred only in structurally intact—and, in this sense, undamaged—cells, but we can press our point a step further. There were on hand in the laboratory the kidneys of some of Doctor Addis' rats that had recovered from transient clamping of the renal artery, which had destroyed portions of the proximal convolutions. Regeneration over three weeks' time had replaced the original epithelium with atypical tubular cells, the most striking structural peculiarity of which is that they possess no rodlets (8). Otherwise they show no structural evidence of "ill health" and they certainly in this sense can not be considered "damaged." These rats with such atypical regenerated proximal convolutions had been suffering from a heavy albuminuria since the experimental clamping of their renal arteries, but as seen in Figure 14 the regenerated cells contain no droplets, though the original cells of other portions of the tubule which had escaped the original damage were filled with them.

Apparently the presence of absorption droplets in the renal cells is therefore

not evidence of damage but proof of a certain functional and structural intactness.

*Observations of the Cytological Changes in Living Cells.* Many of us can remember the feeling of assurance that came to cytologists with the increasing confirmation of their observations on fixed and stained tissues by the examination in various media of living cells. In this country the investigation of Lewis and Lewis and of Sabin are brilliant examples. These methods can be applied to our problem, and today with greatly increased efficiency by the use of phase microscopy.

Scrapings or teased bits of the cortex of a rat that had been given egg white were suspended in rat serum, Locke's solution or 0.9 per cent NaCl, and examined under the phase microscope. For a certain time (15 to 30 minutes) no change is observed in their structure that would indicate that they are not living; then, the typical alterations of cytoplasm and nucleus are observed which are known to indicate cell death (9). The physical changes due to the mechanical differences of their existence free in a fluid medium, rather than under the orienting forces that exist in the continuous layer which lines the tubule wall, are very great, for the cells become spheres and the rodlets are no longer aligned in palisade form by the lateral pressure of contiguous cells. However, we shall again be able to follow the inverse ratio of rods and droplets in these living preparations.

Figures 16 to 19 are from the proximal convolutions of a control rat which had received no egg white. In Figure 16 the nuclear pattern of the chromosomes and the nuclear membrane is intact and similar to what is seen in fixed and stained preparations. The rounded cytoplasm is filled with what appears to be short, tortuous or kinked thick rods, as only a small section of the long disoriented filamentous rodlets can be seen in the single optical plane of the photograph. There are no droplets present. With the passage of time, the cells change; the nucleus swells, its detail becomes clouded and its membrane less sharp, and protoplasmic extrusion occurs (figs. 17 and 18). There is a progressive change in the hook-like rods which swell to rounded figures so that in the end the cytoplasm is filled with small spherules (fig. 19).

The appearance in the living cells from the tubules of rats that are absorbing egg white is quite different (figs. 20 and 24). In Figure 20 is seen a cell whose cytoplasm is distended almost to the point of rupture with large droplets which by the phase contrast effect show varying degrees of density from solid black to light grey. There are no traces of the hooked rods of the normal cell. In Figure 21 a similar cell has been crushed and in this thin preparation the nuclear details and clustered droplets of varying size and contrast are more clearly evident. In Figure 22 is shown a cluster of three cells, two filled with droplets and another with a well preserved nucleus. The latter cell contains few, if any, droplets but the tangled pattern of filamentous rodlets is especially well seen. Figures 23 and 24 show cells filled with large droplets, the first with a still intact, but swollen, nucleus and a beginning cytoplasmic blister, the second obviously dead, with only the remains of a disintegrated nucleus and a great cytoplasmic extrusion.

Observation of the living cells, therefore, shows not only the inverse relation of rodlet and droplet in the absorbing cell but also, as a comparative glance at

Figures 19 and 20 will show, that there can be no possibility that the droplets are merely swollen or "degenerating" rodlets.

Another method at our disposal for the examination of living cells is the method of supravital staining. Under the cover slip, the living cells are brought into contact with dyes, in particular neutral red and Janus green. The significance of the reaction with the former is a complex question with which we need not concern ourselves at this time; staining with *dilute* Janus green in concentrations of 1/25,000 to 1/50,000 is generally admitted to be a reaction specific for the mitochondria of all cells. Even biochemists admit this color reaction to be the ultimate criterion for the identification of these particulate components of the cytoplasm.

Kidney cells and even portions of proximal convolutions can be teased in 0.9 per cent salt solution which contains these two dyes. From many preparations an occasional successful penetration of the tubule by dye will succeed in showing the cytoplasmic components clearly stained in the living cells. Figure 25 shows a portion of proximal convolution from a control rat which had received no egg white after immersion for 5 minutes in 0.9 per cent NaCl containing a concentration of 1/35,000 Janus green. The unstained nuclei, presumptive evidence that the cells are not dead, are surrounded by long rodlets which—considering the difficulties inherent in photographing a thick, unfixed and uncleared tubule—reproduce in a remarkable manner the appearance of these structures as seen in the conventional fixed and stained section. It should be noted that the only elements in the cells stained by Janus green are the rodlets.

In Figure 26 is shown a similar preparation from a rat which had received egg white. No filamentous rodlets are seen, but the tubule cells are obscured by the mass of droplets streaming out from the tubule, which was ruptured by the pressure of the cover glass. Most of these droplets are tinged with dye, so that some appear quite dark while others are almost colorless.

In the recording of our observations we have made a special effort to use the objective procedure of photography whenever possible, but oil-immersion kodachromes accurately recording the delicate colors of these living cells floating free in a suspending medium are impossible. In Figures 27 to 35 are seen the details of supravital preparations as they were observed and drawn by my coworker, Muriel MacDowell. They show with accuracy what is seen as the constant shifting of focus during visual examination reveals the various optical planes of the spherical cell. Figures 27 and 28 show isolated renal tubule cells from control rats that were stained with 1/35,000 Janus green. The dark green, almost black, stained mitochondria are evident as rodlets or irregular particles, and the brushborder, indicating the origin of the cell from the proximal convolution, is seen in one cell in an unusual configuration due to the lack of orientation of its original location. In Figure 29, from a spontaneous albuminuria, are a few small droplets, perhaps of absorbed plasma protein, along with rodlets. In the combined stain of neutral red and Janus green it is seen that the mitochondria are green, but that the droplets are both red and green.

Figures 30 to 35, from a rat which had received egg white, are cells distended with large droplets. In our method of supravital staining the cells may be



placed under the cover slip in 0.9 per cent NaCl and the dyes run beneath the glass by capillary. In Figures 30 to 33, and 35, Janus green preceded the neutral red, while in Figure 34 the neutral red was used first. It is evident that egg white droplets stain predominantly with the dye which reaches them first, and there is evidence, therefore, of competition for the dye. Other droplets, however, indicate by their dull purplish color that both dyes have been "absorbed."

Postponing for the moment any inference from these observations with supravital staining, let us simply state that the rods and droplets differ in their reaction to the two stains in that the former react only to Janus green, while the droplets stain with both.

Staining of tissue cells is a method of analysis that leaves many unconvinced who are quite willing to accept the significance of color in a test tube. There are, of course, many and some good reasons for this attitude, though it may at times irk the morphologist to see his "histochemical" reactions treated with skepticism. But morphologists may be proud that among their confreres there are those who have shown the way to the resolution of these uncertainties. I refer to the fundamental technique introduced by Bensley and by Claude for the isolation of cytological constituents, by an integration of biochemical and cytological methods, into what promises to become a "cytochemistry" *sans reproche*.

*Observations on the Chemical Constitution of the Cell Elements.* As was seen in Figure 26, when the egg white droplets escape from a crushed tubule into the surrounding salt solution they do not dissolve, but maintain their configuration. This makes it possible to apply to renal cells the current methods of preparation of homogeneous suspensions of cytoplasmic particulate matter. Since we are concerned with mitochondrial rodlets of filamentous form and with large droplets of spherical contour, it is essential that a method be used which will preserve unaltered the physical configurations of both elements. The introduction of 0.88 Molar sucrose by Hogeboom, Schneider and Pallade (10) as a medium for the suspended particles has solved this problem.

The exact procedure of the preparation of the homogeneous suspensions may be left for future detailed publication. In brief, renal cortex is ground to a pulp and suspended in 0.88 Molar sucrose solution. Repeated centrifugations at proper speeds and length of time with resuspension in fresh sucrose solution results in the removal of gross debris and nuclei and increasingly homogeneous suspensions of the two cell elements, rodlets and droplets. The entire procedure is done under refrigeration at less than 4°C. to prevent enzymatic alteration of the material.

The results of the preparations are shown in Figure 36, which shows samples of the suspensions in smear preparations stained with methyl violet. In Figure 36A is seen an impure mixture of droplets, mitochondria and cellular debris from the earlier stages of the preparation. The final suspensions of droplets and of mitochondria are shown in 36B and 36C, the former presenting a tangled mass of short rod-like mitochondria, the latter a pure suspension of the large droplets.

When the two particulate constituents of the renal cells in their sucrose suspension are stained with the Gram method they are found to be Gram-positive. It will be remembered that in the histological sections the droplets were Gram-

positive but the rods Gram-negative. This discrepancy is due, of course, to the treatment of the mitochondrial structures before they are stained. Our demonstration that the mitochondrial rodlets of the renal epithelium are Gram-positive—under what may be considered a less altered condition than obtains in the fixed specimen which has been treated with alcohols—suggests that they may be the source of the cytoplasmic component of the droplet which was provisionally identified by enzyme action as ribonucleic acid.

Such speculations, however, can now be dismissed for the morphologist has handed to the biochemist (without, I assure you, resigning his personal interest and opportunity for participation in the work) samples of rodlets and absorption droplets for purification and analysis. Dr. Werner Straus is presently examining, by a combination of microchemical and serological methods, the partition of egg white protein between the cellular constituents. At this time I shall say only that his preliminary examinations show that it is concentrated in the droplet fraction, but that it forms only a part of the nitrogen-containing material of the droplets. As the morphologist suspected, some nitrogen-containing element other than absorbed egg white constitutes a considerable portion of the substance of the droplet, and there would seem no other source for this than the constituents of the cytoplasm of the cell.

There is reason, I think, for a special optimism in the application of these methods to our particular problem. Our rodlets and absorption droplets are specific structures, concerning which we have definite knowledge, and we can therefore form reasonably founded hypotheses on which investigation can proceed. For example, we can cause and control the droplet formation, varying the nature of the absorbed protein component to suit the requirements of our experimental procedure. This is in marked contrast to the investigations of cytoplasmic particulate matter where such indeterminate objects as "secretion droplets" in the liver cells, concerning whose nature or function little is known, are subjected to study.

At this point we should, I think, summarize our factual findings and see where they have led us. First, the bare facts:

1. Egg white filters through the glomerulus and appears in the urine.
2. During this excretion droplets appear in the cytoplasm of the cells in the middle third of the proximal convolution, but not elsewhere in the nephron.
3. The analogous and identical appearance within the cells of droplets of easily identified dyed protein or hemoglobin leaves no doubt that the droplets of our experiments are the structural evidence of the absorption of the egg white. Preliminary serological tests have indeed shown that they contain egg white.
4. Concomitant with the appearance of the droplets, the mitochondrial rodlets dissolve and disappear in this segment of the proximal convolution but remain unchanged in other parts of the convolution.
5. The only Janus green-positive element in the living cells of the proximal convolution is the mitochondrial substance of the rods. These are negative to neutral red.
6. The droplets in the segment of the proximal convolution where the mitochondrial rods have disappeared are also found to be Janus green-positive. They



are also Gram-positive, as are the mitochondrial rodlets when examined in fresh particulate suspensions. Finally, the droplets stain with neutral red.

7. Egg white is neither Janus green-positive nor Gram-positive; it stains readily with neutral red.

8. Those renal cells of a nephron which have been damaged by a toxic agent do not show the formation of droplets, though the contiguous cells in the same nephron which have escaped that damage are filled with droplets.

From these facts I would conclude, first, that the droplets are not constituted of absorbed protein (egg white) alone but contain an admixture of mitochondrial (cytoplasmic) material. The functional significance of this combination we may leave to my final conclusions. Secondly, since damaged or immature cells do not show these cellular reactions, we can not consider the presence of droplets in renal cells as evidence of cellular damage, but rather proof of a certain vitality of the renal epithelium.<sup>4</sup>

Our description of the structural aspect of the entrance of proteins into the renal cell, with its explanatory gloss of hypothesis concludes what we have learned about the first phase of the metabolic handling of these substances by the nephron. The next logical step would be to examine what happens to the absorbed droplets of protein.

It has long been known that they break down and disappear, some fairly rapidly [as is the case with hemoglobin droplets (11)] others very slowly, over a matter of weeks [egg white for example (3)]. Though our group is considering certain aspects of this complex problem—for example, the localization of enzymatic activities in our preparations of mitochondrial rods, droplets and microsomes from renal cells that are absorbing protein—you will understand that the limitations of time and your patience will lead me to confine my discussion to the simpler first stage of the metabolic process.

The mention of the breakdown of absorbed intracellular protein calls to mind a group of related metabolic products which are constantly handled by the kidneys. To quote Peters and Van Slyke (12), "These organs occupy a unique position" in the metabolism of the amino acids. You will not expect from a morphologist a critical summary of these matters, nor do the provisional and elementary contributions to the structural aspect of the problem that I shall describe need more than a brief recalling of certain pertinent data on how the kidney handles these substances.

1. *Absorption and Storage in the Kidney.* In the classic demonstration of Van Slyke and Meyer (13), it was shown that following the administration of amino acids there occurred a concentration of amino-acid nitrogen in the liver above that of the general tissues and that this fell to the general level in a few hours. The kidney, however, stood between the liver and the muscles in its behavior, and in certain experiments resembled the liver, for a brief but definite period, in its capacity to absorb and store amino-acid nitrogen.

2. *The Selective Excretory Function of the Kidney.* Amino acids from the blood

<sup>4</sup> Their presence in the renal epithelium is, of course, evidence that the tubule fluid contained protein. This may have been due to excessive (abnormal) filtration of serum proteins and indicative of "damaged" glomeruli, so that the "hyalin droplets" are still useful to the pathologist.

filter readily through the glomeruli, yet only small amounts appear in the urine. Pitts (14) has recently demonstrated the individual differences in this resorption process as it concerns various amino acids. Beyer, Wright, Skeggs, Russo and Shaner (15) have followed by means of renal clearances the detail of the process, with the demonstration of competition for absorption between certain of them.

3. *The Specific Syntheses Occurring in the Kidney.* The formation of ammonia from glutamine and possibly other forms of amino N, of guanido-acetic acid from arginine as a precursor to creatine formation in the liver, and the conjugation of benzoic acid with glycine in the kidney of the dog are examples of localized synthetic renal activity.

4. *The Enzymatic Activities of Kidney Tissue.* I need only list a few of the many enzymes which have been demonstrated in kidney tissue, such as alpha-amino acid oxidase, glutaminase, histidine decarboxylase, proline oxidase and tyrosine decarboxylase.

5. *The Toxic Action and Protective Effect on the Kidney.* A recent striking example is the demonstration by Wachstein (16) of the destructive effect of *dl*-serine on the terminal portion of the proximal convolution and the protection from this damage afforded by the administration of methionine and certain other amino acids.

Hitherto the morphologist has had little or nothing to offer in the way of a structural framework to support this mass of functional knowledge; in a consideration of the part the renal elements play in these dynamic processes our thinking operates in what might be described as a total structural void.

What I shall offer this evening may well be considered an unstable foundation for the functional superstructure, particularly since its argument depends on analogy. It consists of a demonstration that during the absorption of amino acids by the tubule of the nephron intracellular changes occur in the renal epithelium similar to those I have described as accompanying the absorption of proteins. In considering the validity of the analogy between these structural changes certain differences between the properties of the amino acids and the proteins should be kept in mind, namely, 1) the simplicity of structure and small size of the amino acids; 2) their more rapid metabolism within the renal cells; and 3) the consequent transitoriness of any possible concentration of them in the renal cell as compared to the slowly metabolized proteins, this being due either to the rapidity of the intracellular metabolic process by which they are altered or to their passage into the blood stream.

The procedure of our investigation of this problem was similar to that of the preceding experiments with proteins. Various amino acids were added to the stock diet in concentrations up to 10 per cent and after three to seven days on this regimen a booster dose of the amino acid was administered intraperitoneally. Two to four hours later the animal was killed and the renal tissues examined. We can briefly run through a description of the structural changes seen in the nephrons and their constituent cells, for, as I have said, they are similar to what I have described before; moreover, no significant differences were observed after the administration of the different amino acids.

In sections stained with iron hematoxylin after Zenker fixation the previously

described alteration between rods and droplets was found in the proximal convolutions. The droplets were, however, smaller than those observed after the injection of egg white, and the renal cells were never so distended by them (fig. 37). If the sections were Gram stained, then, as before, the rods did not retain the dye, whereas the fine droplets were strongly Gram-positive (fig. 38). Dissected proximal tubules stained by the Gram method showed the tubule cells filled with finely dispersed, small droplets. Their distribution was definitely more extensive than was observed in the proximal convolutions absorbing egg white protein, for their entire length, including the terminal portions, was equally filled. No differences could be noted in this distribution when different amino acids were used (fig. 9).

The disclosure that fine Gram-positive droplets appear in the renal cells after the administration of amino acids requires a brief reconsideration of the observations made by this method in the demonstration of the egg white droplets, for amino acids are being absorbed by the renal cells constantly under physiological conditions; the fine droplets should therefore be present in all kidneys. In pointing out the Gram-negativity of the rods in the control kidney of Figure 7, for the sake of my exposition I did not emphasize the few scattered, minute, Gram-positive structures that can be seen in the renal cells. Viewing them in the thickness of a dissected proximal convolution from a control animal on stock diet their number becomes considerable (fig. 10). Similarly, they can be seen in the dissected preparations interspersed between, and in most part obscured by, relatively enormous Gram-positive droplets of egg white.

When living cells were observed in physiological solutions by the phase microscope, the cells from proximal convolutions of the animals which had been receiving amino acids were filled with droplets. The droplets which had replaced the short, thick, optical segments of the rods were smaller than those seen after egg white absorption (figs. 39 to 47). Another difference noted was that the droplets, following the amino acid injection, swelled, apparently from the imbibition of water, so that after fifteen to twenty minutes the cells were distended with large droplets. There was, however, no apparent increase in the number of the droplets. Usually nuclear changes accompanied this alteration (figs. 44 to 47).

The most striking demonstration of the appearance of rods and droplets in the tubule cells was obtained, however, by the examination of unstained frozen sections of tissue recently fixed in 10 per cent formalin. It is possible to fix the isolated living cells with weak formalin while they are being examined with the phase microscope. The action of the formalin produces definite changes. These consist of a sharpening of detail in the cellular structures as the protoplasmic elements are denatured, but it can be definitely observed while the process is occurring under the eye that no structures similar to rods or droplets result as artifacts or products of the fixation.

Figures 50 to 57 show, first, the appearance of cross sections of proximal convolutions three hours after the injection of the following amino acids: *dl*-isoleucine, *l*(-)-leucine and glycine; and, second, a control animal. For comparison, the appearance of similar sections containing egg white droplets is also shown (fig.



48). Other amino acids, *l*(-)-tyrosine, *l*(+)-arginine monohydrochloride, *dl*-tryptophane, *l*(+)-histidine monohydrochloride, *l*(+)-glutamic acid, *dl*-methionine and *dl*-phenylalanine are not shown but presented the same appearance.

In Figure 49 the section is taken from a rat on the control stock diet; the unstained rodlets are clearly seen and predominate over a moderate number of droplets. In the remaining figures rodlets are only rarely seen, though in Figure 55 (from the rat which received glycine) they still predominate in the basal portion of one part of the tubule where the droplets are scanty. Perhaps even more strikingly than in the previous figures these illustrations emphasize the necessity of the use of varying phase contrasts in the examination of a tissue if one is to feel confident that he has seen all the structural detail contained within the specimen. Moreover it is plainly apparent from a comparison of the photographs taken with objective 3.0 B— and with the other two optical systems that a differentiation can be made between droplets that are otherwise similar, for many of these objects that appear with the last two systems are absent with the first. The physical or chemical properties responsible for this optical difference are, as far as I can learn, still unknown.

#### CONCLUSIONS

Before proceeding to the conclusions which I shall advance from what has been presented this evening, I wish to recall the results of work done some years ago in my laboratory on what is generally considered the converse of the tubular process of resorption, namely, secretion. The physiologists find it useful to consider these two tubular functions together in their theories of mechanism as expressions of cell transport.

It is possible to study very exactly, by what I have called the extra-vital method, both the functional and structural changes during the secretion of neutral red by the tubules of the perfused frog's kidney (17). The procedure is as follows: both kidneys of the pithed animal are perfused by the aorta and renal-portal system with modified Locke's solution containing sugar. A sugar-free, hypotonic "urine" is formed and under the conditions of the experiment we can be certain that nothing is being secreted and only sugar, water and electrolytes absorbed. One kidney is removed, fixed and stained with iron hematoxylin for morphological study, but the perfusion of the remaining kidney is continued after adding neutral red to the renal-portal system; the dye is then secreted in high concentration. This kidney is then fixed and stained with the same method and the structural changes compared to those of the first kidney, which was not secreting. Figure 58 shows cellular alterations similar to those we have observed in the absorption of egg white. In A are seen the intact filamentous rodlets of cells in what is the analogue of the mammalian proximal convolution. These tubules were not secreting anything and were absorbing only water, sugar and electrolytes. In B, concomitant with secretion of neutral red, the rods have disappeared and the cells are filled with droplets. The droplets are deep red from the concentration of the dye. In C is shown another segment of the frog nephron, analogous to the mammalian distal convolution, and no droplets or other changes are seen in its cells. In Figure 59 it is seen that the non-secreting tubule of the first kidney (A) is free of Gram-positive droplets, while the cells of the second (B),

secreting the dye, are filled with them. Reference to the colored plate of the original article will show that the phenomena of supravital staining with Janus green and with the secreted neutral red are similar to those I have described in the experiments on the absorption of egg white.

On the strength of what he has shown you the morphologist is now willing to conclude that in the rod-droplet transformation within the functioning renal cells we are seeing one structural aspect of a cytological mechanism of transport and storage which can operate in two directions. During both the secretion and absorption of certain materials by the renal epithelium there occurs a common intracellular structural change which results in an increase in the concentration of the transported substance within the cell. The essential mechanism of this concentration consists of a combination in droplet form of the transported material, dye or protein, with a specific intracellular constituent, the mitochondrial substance of the rodlets. If the renal cells are lacking in this essential mitochondrial substance, as regenerated cells are, we have seen that no absorption by droplets occurs.

What follows upon the concentration of the substance within the cell varies with its nature. If it is a physiological entity of relative simple form, such as an amino acid, it is promptly metabolized or possibly passed on to the blood stream unchanged. More complex materials, such as hemoglobin (11), which only under unusual circumstances reach the tubule lumen, are more slowly metabolized, and a foreign material such as egg white (3) requires weeks for its final disposal. We have seen that the animal's own serum proteins are similarly handled when they reach the tubule lumen in considerable concentration; whether there may occur a constant, "physiological" absorption of lesser amounts of plasma proteins remains still in the realm of the undemonstrated, but such an absorption in non-visible form seems not improbable.<sup>5</sup>

The logical necessity that called to the mind of the functionalist Shannon (18) the hypothetical intracellular X-substance to serve as a link in the mechanism of transport and intracellular concentration of other substances than we have discussed tonight has been recently considered from the viewpoint of its possible operation in the secretion of ascorbic acid by the renal tubule (19). If the morphologist in the special case that he has examined suggests a similar mechanism, his evidence to the present can only be that, "that is the way it looks to me." The future, however, seems to promise him a surer position, for if what he has said tonight of the structural aspect of the metabolic processes in the nephron seems excessively speculative, he now has his rodlets and droplets in a tangible form that can be subjected to the rigors of biochemical technique. Until the findings of these examinations are added to his structural descriptions he is willing that his conclusions be considered tentative. In the meantime he can feel the satisfaction that he is, as in Janeway's time, at his proper job of a pioneer—not, perhaps as in the grand old days, "preparing the way," but in the lesser but still essential rôle of "consolidating the line."

<sup>5</sup> The same problem exists of a secretion of neutral red in non-droplet form, though here experimental demonstration is possible. This I have termed, perhaps not too aptly, "direct" secretion to distinguish it from the "indirect" transport associated with intracellular concentration of the dye in droplet form (20).



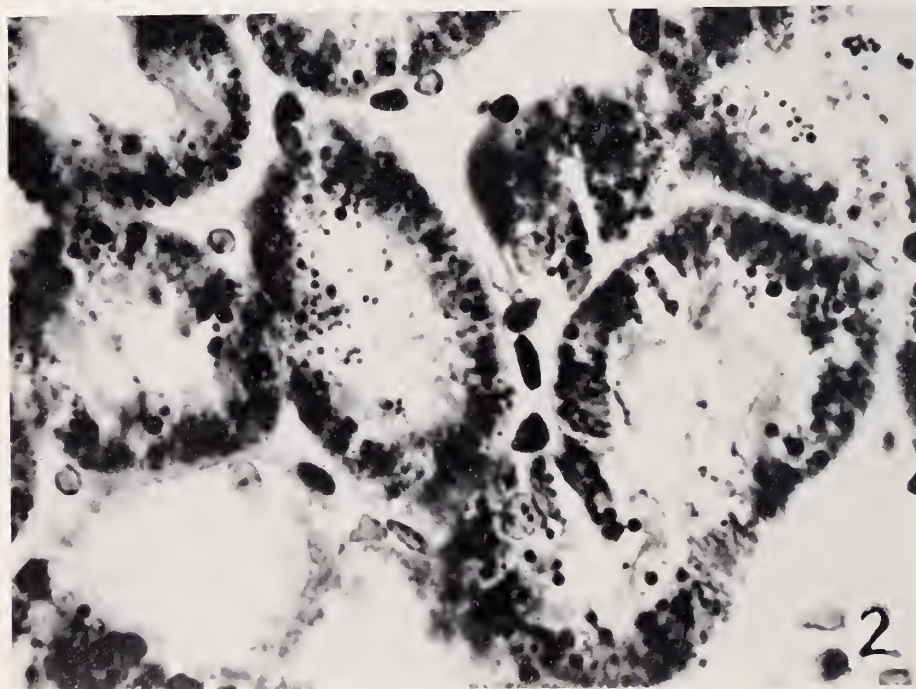
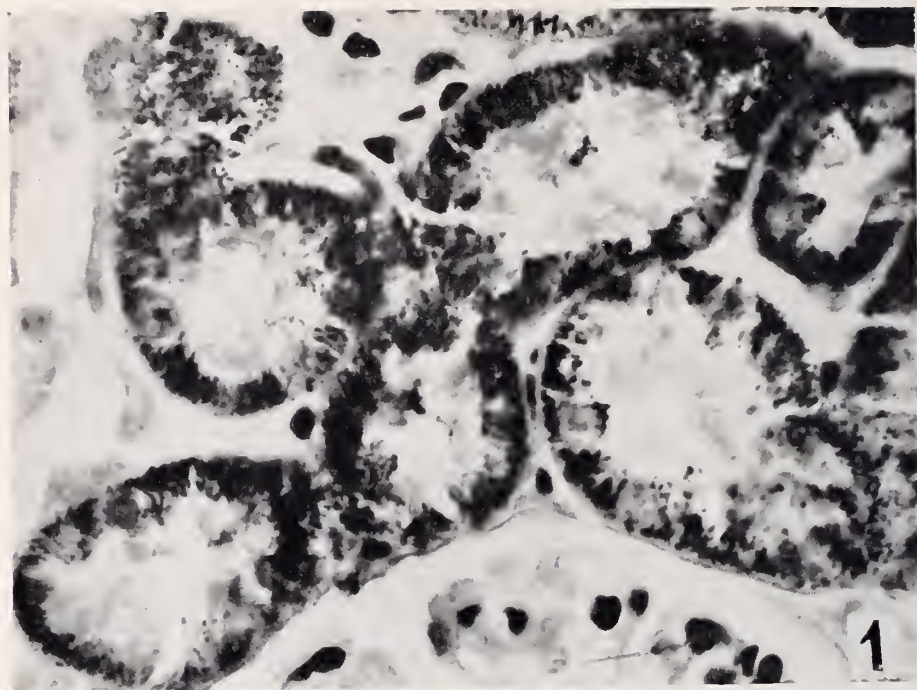


FIG. 1. Cross-sections of a proximal convoluted tubule from a control rat, which had received no injection of protein, showing the rod-like batonnets. Zenker fixation and iron hematoxylin stain.

FIG. 2. Cross-sections of a proximal convoluted tubule from a rat which had received 1000 mg. of egg white intraperitoneally 18 hours before sacrifice. The rodlets are in great part replaced by droplets. Zenker fixation and iron hematoxylin stain.

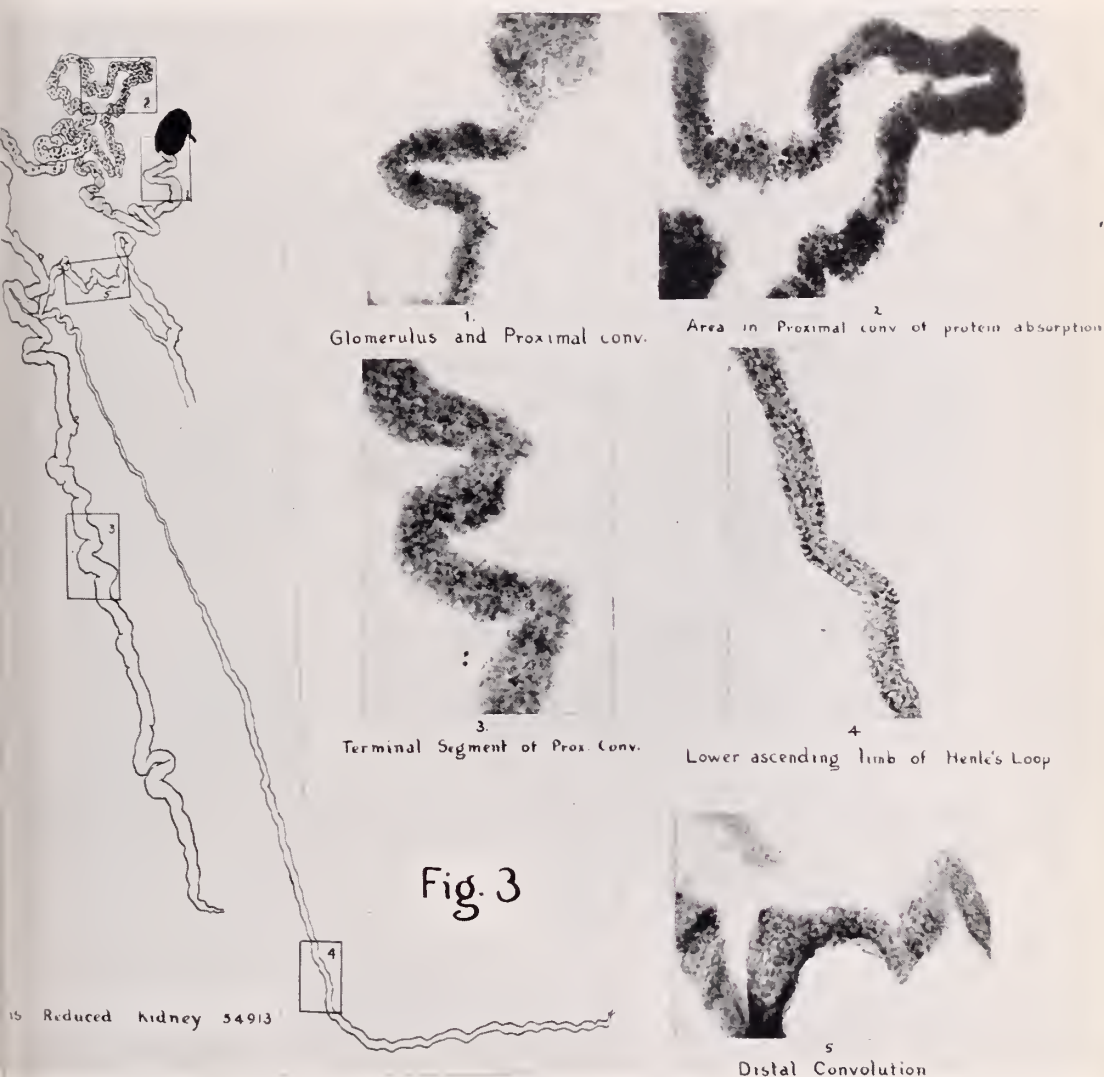


FIG. 3. Camera lucida drawing of a complete, dissected nephron from a rat with a heavy albuminuria which was the result of a  $\frac{3}{4}$  nephrectomy. The site of the droplet formation is shown in stipple in the middle portion of the proximal convoluted tubule. The microphotographs show that the droplets are limited to this portion of the nephron (Cf. fig. 11). Iron hematoxylin stain.

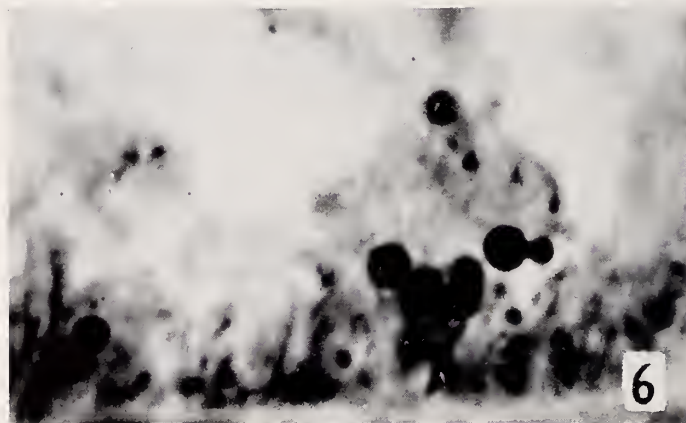
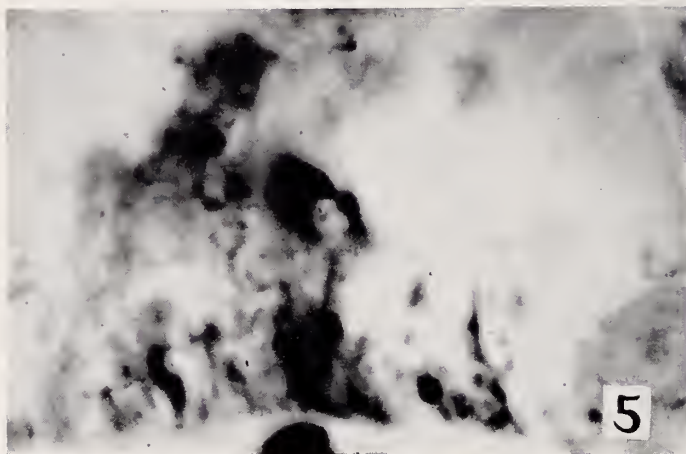
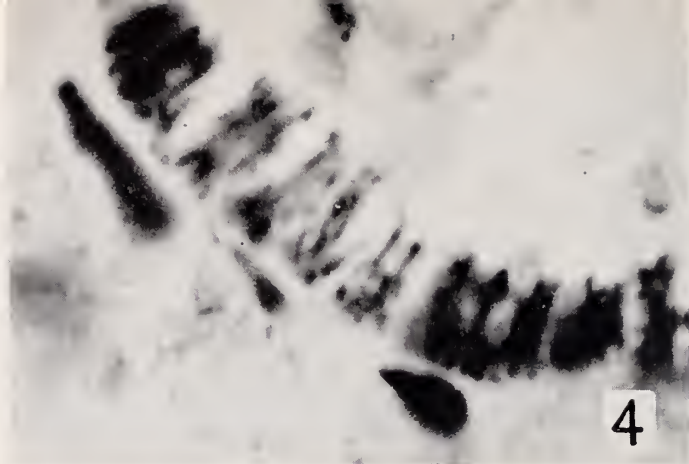


FIG. 4. Detail of the palisade of rodlets in the first portion of a proximal convoluted tubule from a rat excreting egg white. Zenker fixation and iron hematoxylin stain.

FIG. 5. Detail of the cellular changes in the lower segment of the same nephron, showing the swelling and dissolution of the rodlets. A cloud of similarly dark staining material, in which areas of condensation may be seen, surrounds them. Same fixation and stain.

FIG. 6. Similar changes in the same region of another nephron of the same kidney. Definite round droplets are present in the cloud of dark staining material that lies in the region of the dissolving rodlets. Same fixation and stain.



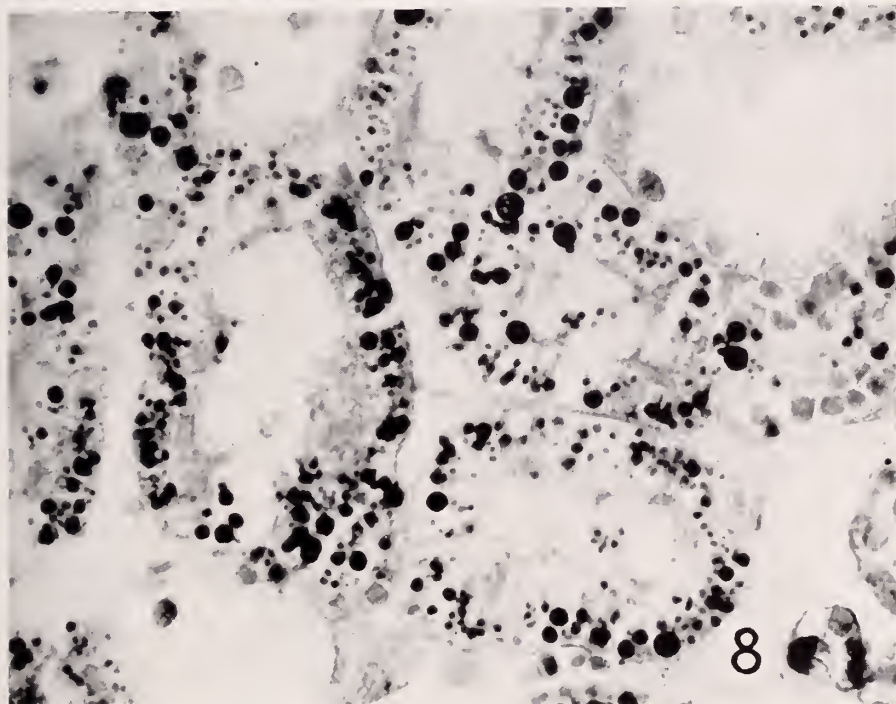
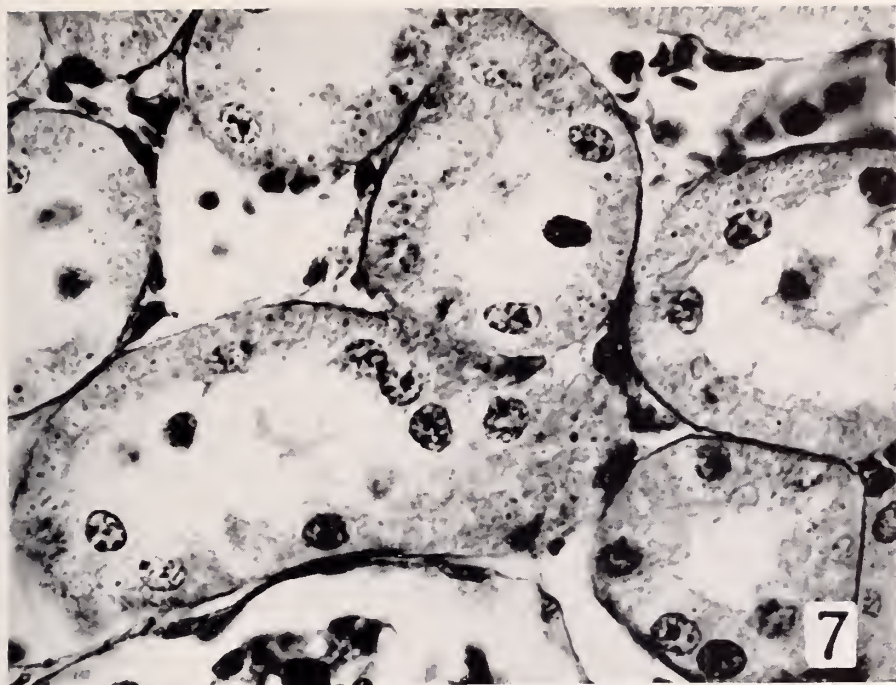


FIG. 7. Gram stain of cross-sections of the proximal convolution of the same control kidney shown in Figure 1. The rodlets have not retained the methyl violet. Zenker fixation.

FIG. 8. Gram stain of cross-sections of the proximal convolution of the nephron excreting egg white shown in Figure 2. The droplets are strongly Gram-positive. Zenker fixation.



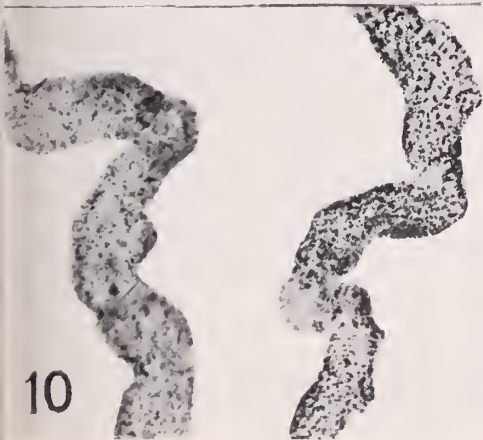
FIG. 9. Dissection of a glomerulus and a complete proximal convolution, mounted and stained with the Gram method, from a rat which had been for 10 days on a stock diet containing 10 per cent *l*(+)-arginine monohydrochloride and which received 10 cc. of 5 per cent solution of this amino acid 3 hours before sacrifice. The entire convolution is filled with fine, Gram-positive droplets.

FIG. 10. Portions of proximal convolutions showing fine, Gram-positive droplets. The tubule to the right is from an animal on a similar regimen of arginine; that on the left is from a control animal on the stock diet. It, too, is filled with dust-like droplets, but to a somewhat lesser degree. Reference to Figure 7 will show that these droplets may also be seen in small numbers in the thin histological section of the tubule.

FIG. 11. Glomerulus and proximal convolution from a rat excreting egg white. As the droplets do not stain with the Gram method, the gradient of droplet formation is more clearly shown than in the microphotographs of Figure 3, where both droplets and rods stained with iron hematoxylin. It will be noted that, departing from the glomerulus, the droplets increase in number to a maximum and then decrease to disappearance.



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FIG. 12. Cross-sections of the upper portion of a proximal convolution from a rat which had received .00075 Gms. of uranium acetate and 3 days later an intraperitoneal injection of 1000 mg. of egg white; it was killed 18 hours after this injection. The epithelial cells are structurally intact and are filled with droplets. Zenker fixation and iron hematoxylin stain.

FIG. 13. Cross-sections of the middle portion of the same proximal convolution. There is extensive damage, with necrosis of some cells, though others whose nuclei are still intact have apparently survived. These damaged cells are filled with disintegrated masses of rodlet debris, some of it in dust-like granular form, but there are no droplets. Same fixation and stain.

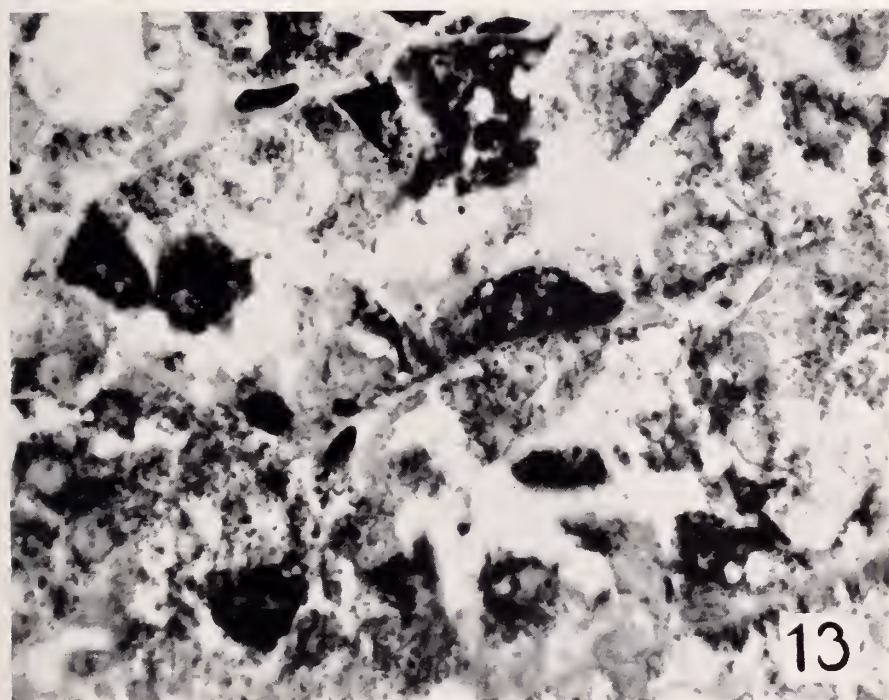
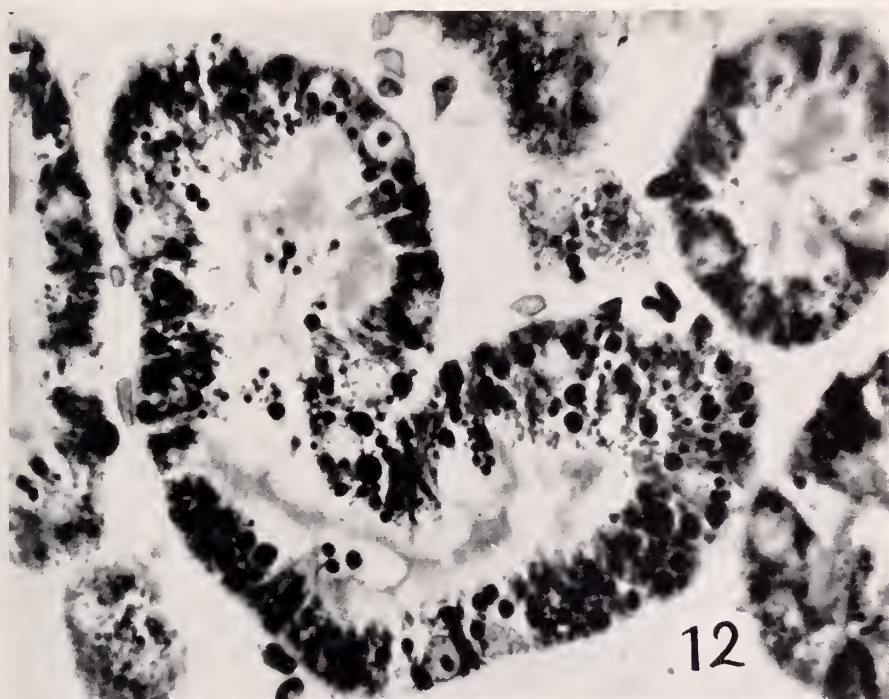


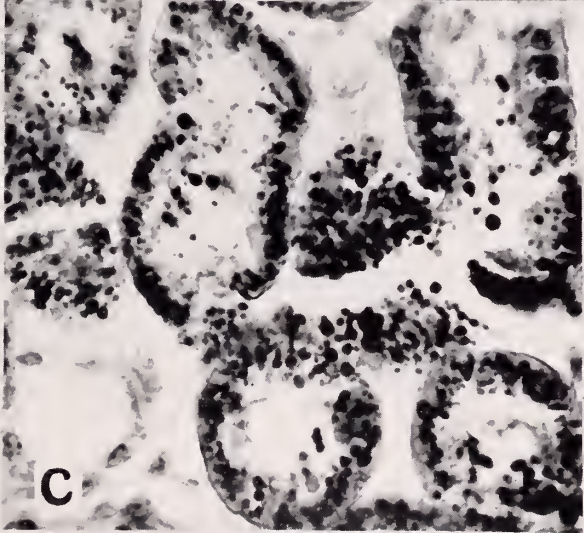
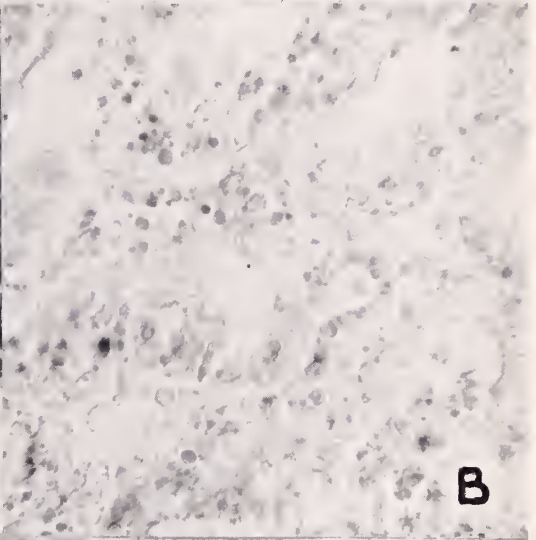
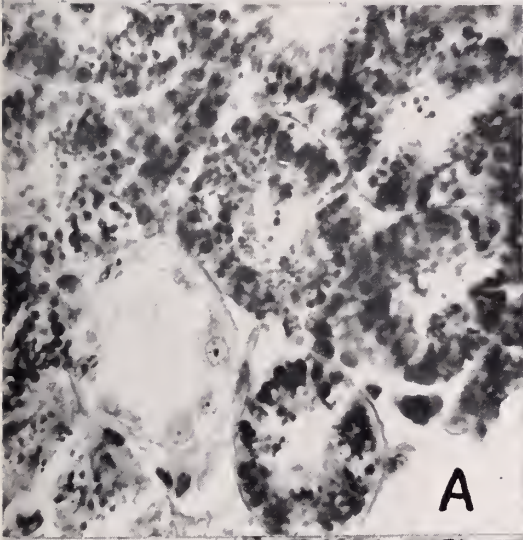
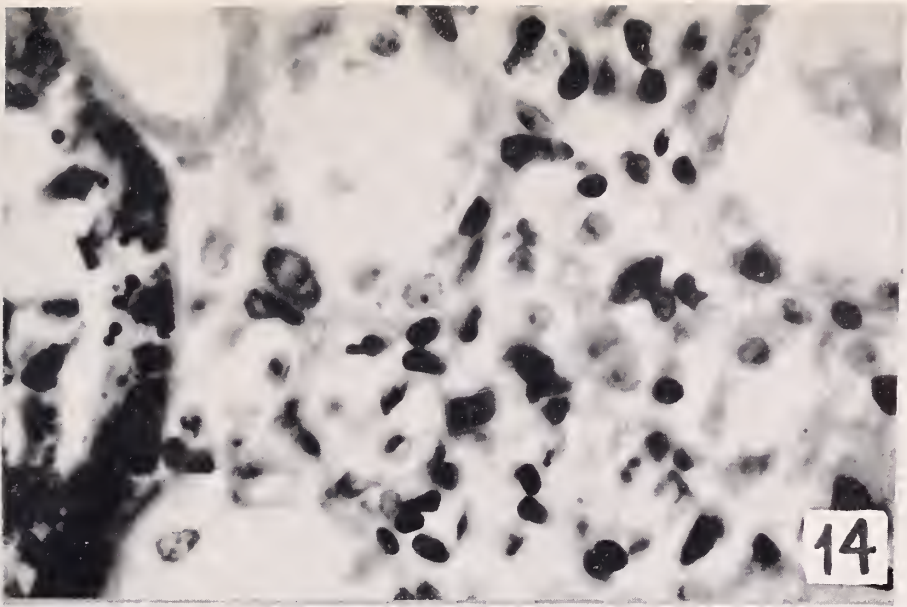


FIG. 14. Cross-sections of regenerated proximal convolutions from a rat which had suffered three weeks previously from ischemic renal necrosis following temporary clamping of the renal artery. At the time of sacrifice there was a heavy albuminuria. The atypical epithelium of the irregularly regenerated tubules (right) contains no rodlets or droplets. A section of the original tubule which had escaped damage (left) contains the usual rodlets, and in it may be seen droplets. Same fixation and stain.

FIG. 15. A. Gram stain of cross-sections of a proximal convolution excreting egg white treated in the control veronal buffer of pH 6.8 at 53° for 3 hours. The droplets are strongly Gram-positive.

B. Gram stain of contiguous section of the same kidney after treatment with veronal buffer containing 1 mg. crystalline ribonuclease per cc.; same time and temperature. The droplets have lost their power to retain the methyl violet.

C. Gram stain of another contiguous section treated as in B and then placed 12 hours in an 0.5 per cent solution of the magnesium salt of ribonucleic acid. The "plated" droplets have regained their ability to retain the methyl violet.



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FIGS. 16 to 24. Microphotographs by American Optical Company phase microscope, oil immersion objective  $0.25 \lambda$  0.14 A — of living unstained cells suspended in 0.9 per cent NaCl solution. (figs. 21, 23 and 24 with Zeiss instrument).

FIG. 16. Cell from proximal convolution of normal control rat that had received no egg white. The nuclear detail is clear cut and the cytoplasm is filled with the irregular dis-oriented rodlets that appear as hook-like segments in the fixed optical plane of the photograph.

FIG. 17. From the same preparation after 15 minutes. The nucleus is swollen but the chromatin pattern is still visible. The hook-like optical sections of rodlets persist, though some have changed to rounded bodies. A protoplasmic extrusion has appeared.

FIG. 18. Same preparation after 20 minutes. The chromatin pattern and nuclear membrane are disturbed. No definite rodlets are seen but only small round bodies.

FIG. 19. Same preparation after 35 minutes. The cell is dead, the nuclear pattern confused and the cytoplasm filled with spherules.

FIG. 20. Cell from proximal convolution of a rat excreting egg white after intraperitoneal injection. The nucleus is intact and there are no hook-like rodlets visible. The cytoplasm is distended with huge droplets, much larger and denser than the spherules which resulted from the agonal changes seen in Figure 19.

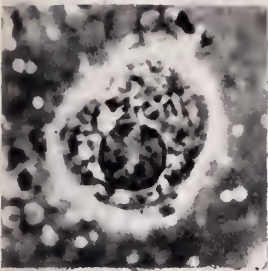
FIG. 21. A similar cell which was crushed by pressure on the cover slip. The nucleus is well preserved. In the thin preparation the dense dark droplets are seen intermixed with lighter appearing optical sections of rodlets.

FIG. 22. From a similar preparation. The large cell (lower left) shows a tangled mass of filamentous rodlets and no droplets. To the upper right, there are two cells filled with large droplets. Their nuclei are poorly preserved.

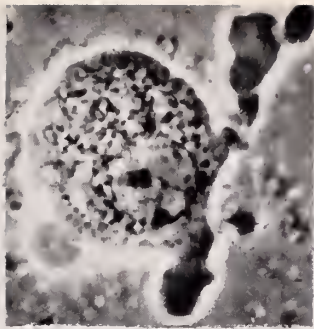
FIG. 23. A cell from a similar preparation. The nucleus is swollen but the nuclear pattern, chromatin and membrane are well preserved. Large dark droplets fill the cytoplasm and a beginning extrusion is seen.

FIG. 24. A dead cell from a similar preparation. All nuclear detail has faded and a large cytoplasmic extrusion is visible. The dark droplets have swollen to twice their original diameter.

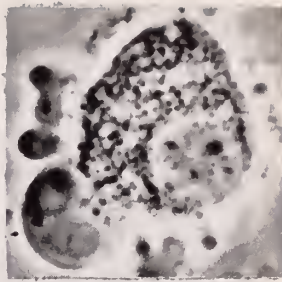




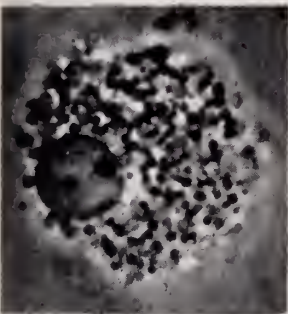
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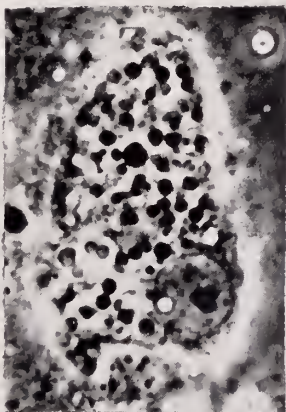
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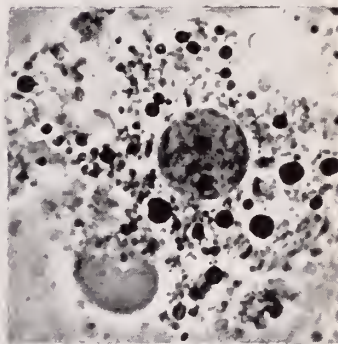
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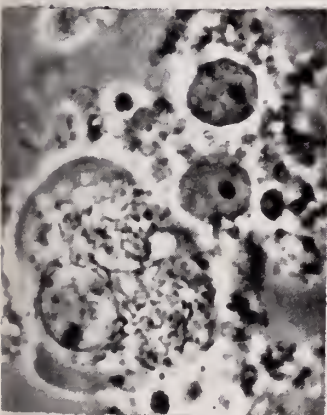
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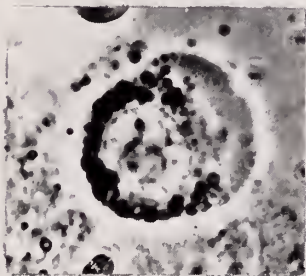
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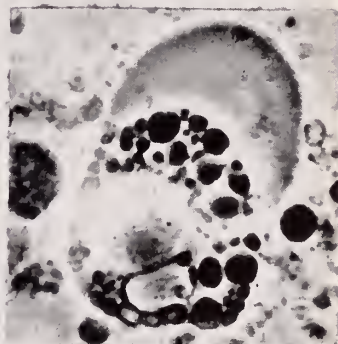
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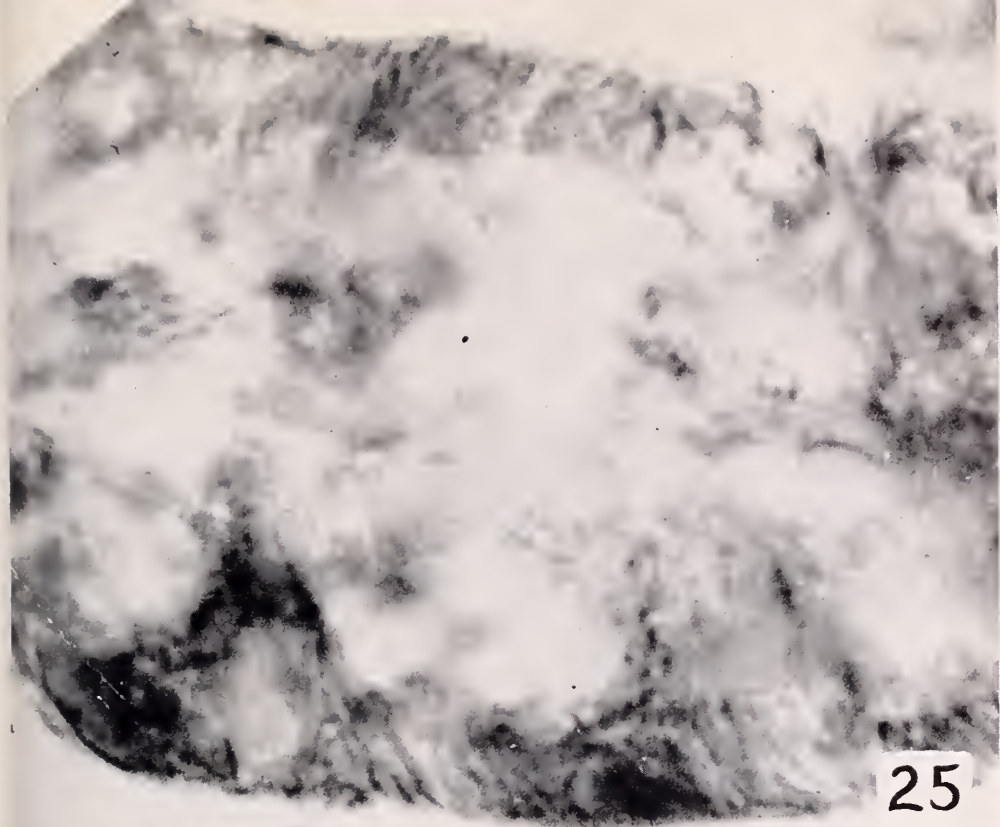


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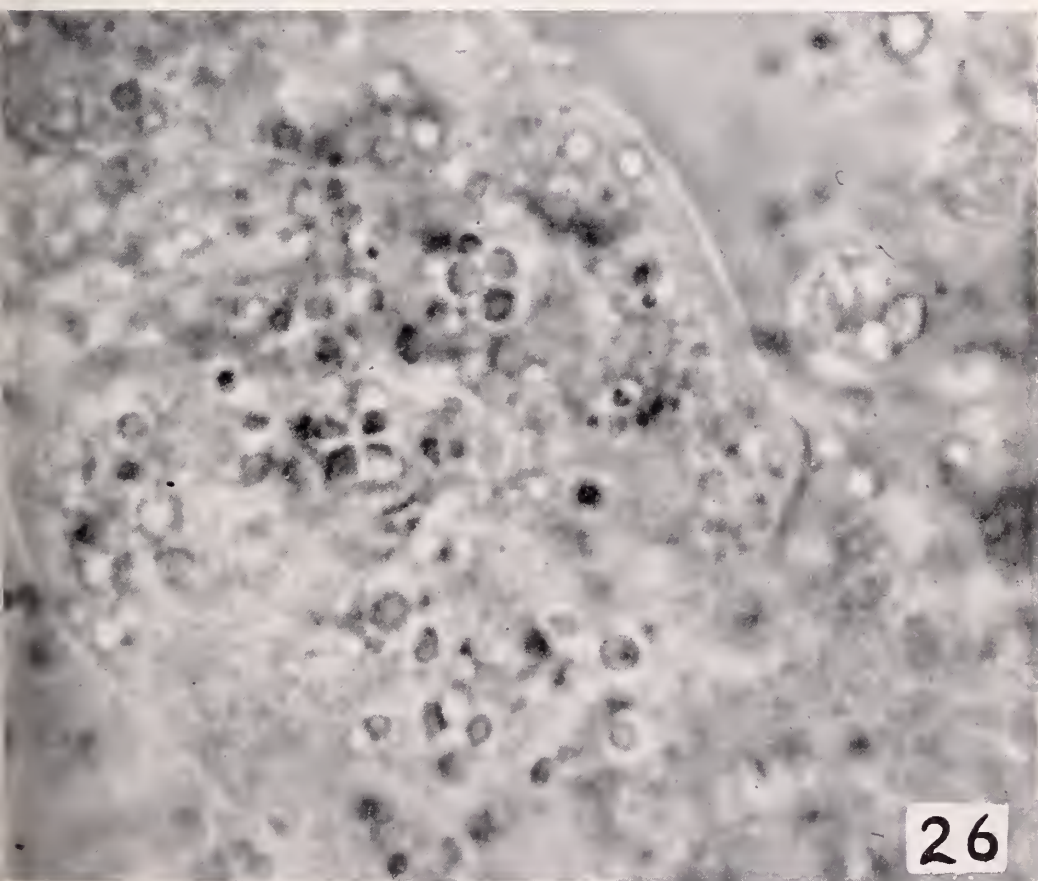


FIG. 25. Microphotograph with oil immersion objective of standard optical design. A segment of proximal convolution (from fresh tissue of a normal control rat which had received no egg white) teased in 1/35,000 Janus green in 0.9 per cent NaCl solution. The tubule was flattened by light pressure on the cover glass. The only stained elements are the long, filamentous mitochondrial rods which surround the open spaces of the unstained nuclei.

FIG. 26. A similar preparation stained with 1/35,000 Janus green from a rat which had been given 1000 mg. of egg white 18 hours previous to sacrifice. The pressure has ruptured the tubule, and streaming out into the surrounding medium are the droplets which have replaced the original rodlets of the renal epithelium. Note that many of these droplets have taken up the Janus green and so appear dark, as contrasted to the bright appearance of the few into which no dye has penetrated.



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FIGS. 27 to 35. Oil immersion (standard optical design) drawings of supravital staining of cells from the proximal convolution. Fresh renal cortex was teased in 0.9 per cent NaCl solution containing 1/35,000 Janus green and 1/10,000 neutral red. In some cases the teased fresh tissue was placed under the cover slip in NaCl solution and the dyes run under the glass by capillarity.

FIG. 27. From a normal control rat. Janus green 1/35,000. The brush border is well seen. Throughout the cytoplasm are scattered the disoriented mitochondrial filaments, stained almost black by the heavy concentration of Janus green. No droplets are present.

FIG. 28. From a similar animal. The rod-like mitochondrial elements are more evident.

FIG. 29. From a similar animal, Janus green and neutral red. A few droplets are seen among the deep staining mitochondria. The droplets stain either light green or red.

FIG. 30. Cell from the proximal convolution of a rat excreting egg white, 18 hours after intraperitoneal injection. Stained supravitaly, first with Janus green and then with neutral red. The cytoplasm is filled with large droplets which stain with the Janus green. One droplet has taken up the neutral red.

FIG. 31. A cell from a similar preparation. A few deep blackish-green mitochondrial rods are present. The droplets are stained both green and red.

FIG. 32. A similar cell containing both green and red droplets.

FIG. 33. Similar preparation. Green droplets predominate.

FIG. 34. The neutral red was used before the Janus green. The droplets are predominantly red.

FIG. 35. A mixture of 2 parts Janus green and 1 part neutral red was used. Most of the droplets are green, but some have taken up both dyes and are a greenish-purple.



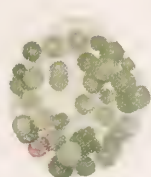
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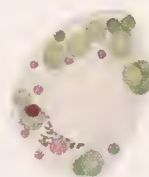
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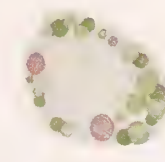
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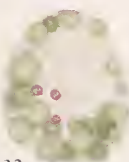
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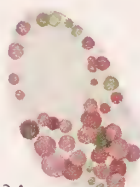
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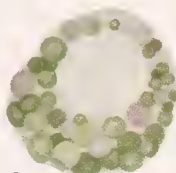
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FIG. 36. Smears of suspensions in 0.88 M sucrose of particulate bodies from the cortical tissue of a rat which was excreting egg white after intraperitoneal injection.

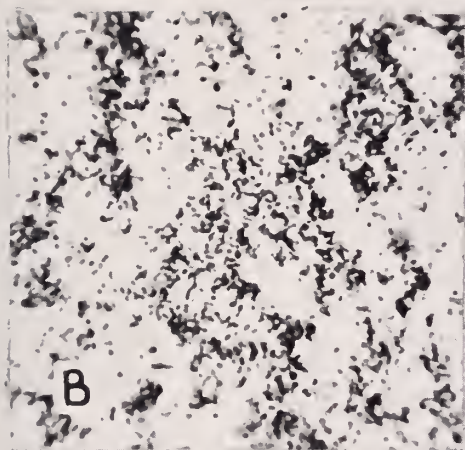
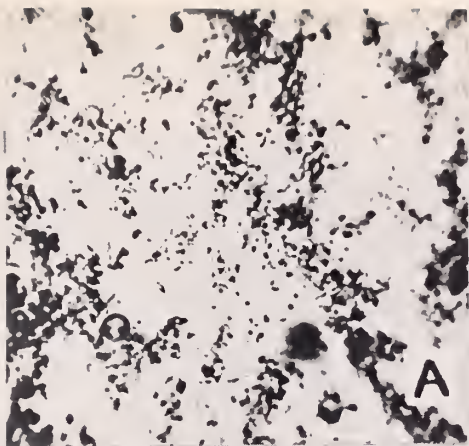
A. At an early stage of the differential centrifugation, the suspension consists of a mixture of rodlets, droplets and debris. Two red cells are also present.

B. The final preparation of mitochondrial rodlets. A few small spherical bodies are present which may be either small droplets or, as their often oval shape suggests, round fragments of rodlets.

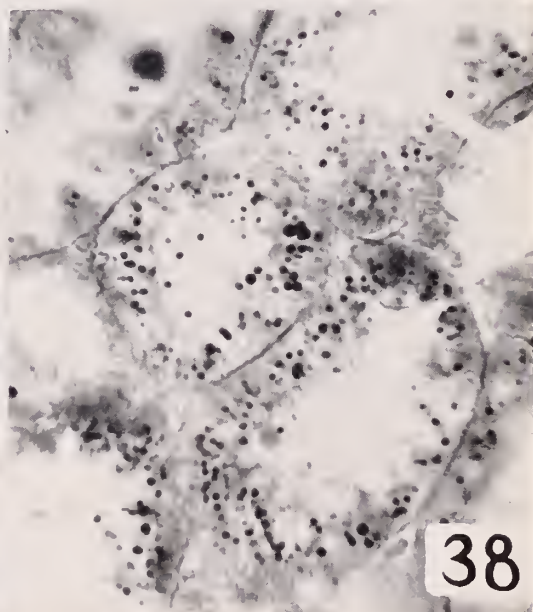
C. A pure suspension of the large droplets. No rodlets were seen in this preparation.

FIG. 37. The rodlet-droplet transformation in the proximal convolution of a rat on a regimen of *dl*-phenylalanine. The same structural changes are observed as in the egg white experiments except that the droplets are much smaller. Zenker fixation and iron hematoxylin stain.

FIG. 38. Gram-positive droplets from the kidney of a rat on a glycine regimen. As in figure 8 the rodlets are not stained; the droplets are smaller than those in the egg white experiment. Zenker fixation and Gram stain.



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FIGS. 39 to 47. Living, unstained cells from the proximal convolutions of rats on an amino acid regimen of tyrosine, observed by phase microscopy. American Optical Co., oil immersion objectives  $0.25 \lambda 0.14 A-$ ,  $0.25 \lambda 0.14 A+$ , and  $0.25 \lambda 3.0 B-$ . For comparison with the appearance seen in control rats on stock diet, see Figures 16 to 19.

FIG. 39. A cell under "dark phase" contrast showing a well preserved nucleus. Its cytoplasm is filled with dark droplets somewhat smaller than those seen in the egg white experiments. No hook-like optical segments of the rodlets are visible. Objective  $0.25 \lambda 0.14-$ .

FIG. 40. The same cell taken under "bright phase" contrast. The optical effect of the previous photograph is reversed. Objective  $0.25 \lambda 0.14+$ .

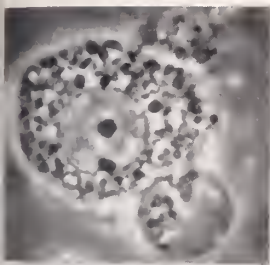
FIG. 41. The same cell under a different value of "dark phase" contrast. Note that not all the dark granules of Figure 39 are visible. Objective  $0.25 \lambda 3.0 B-$ .

FIG. 42. A cell from a similar preparation. The brush border is well shown (Cf. fig. 27). The droplets are small. Objective  $0.25 \lambda 0.14 A-$ .

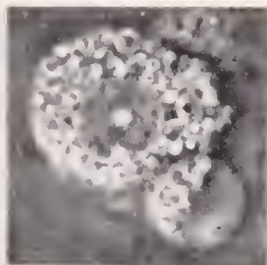
FIG. 43. A crushed cell from a similar experiment. In the thin preparation, both droplets and irregular mitochondrial structures can be seen. Objective  $0.25 \lambda 0.14 A-$ .

FIG. 44. A dead cell from a similar animal. The nucleus (above) is shrunken and pyknotic. The droplets are swollen and there are several cytoplasmic extrusions.

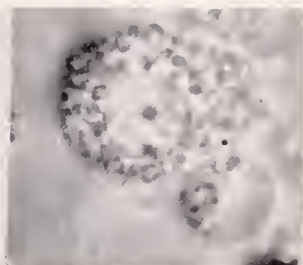
FIGS. 45, 46 and 47. Three phase contrasts of the same cell from the same preparation. The nucleus is pyknotic and the droplets greatly swollen. Note the striking difference in the appearance under the varying phase contrasts. Objective  $0.25 \lambda 0.14 A-$ ,  $0.25 \lambda 0.14 A+$  and  $0.25 \lambda 3.0 B-$  respectively.



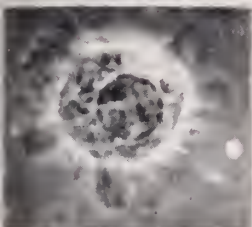
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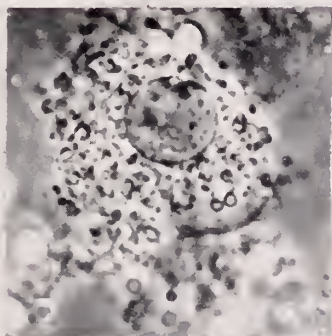
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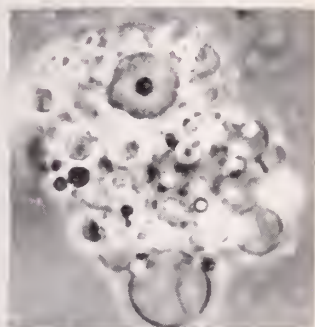
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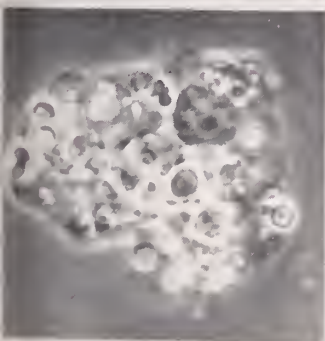
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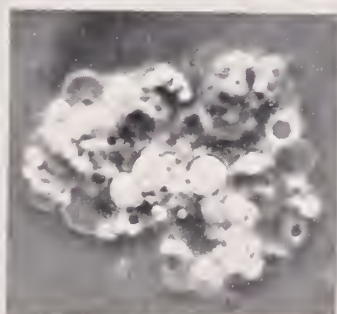
43



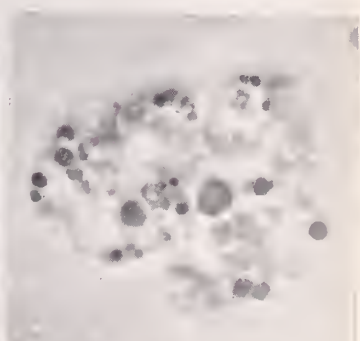
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FIG. 48. Frozen unstained section under "bright phase" microscopy of the kidney of a rat which had been given egg white. The rodlets have almost entirely disappeared and the protoplasm is filled with the large bright droplets. (Cf. fig. 2). The cytoplasm of the cells thus has the appearance of a foamy emulsion, reminiscent of certain cytological theories. Objective  $0.25 \lambda 0.14 \text{ A}+$ .

FIG. 49. A similar preparation under "dark phase" microscopy from a control animal on stock diet containing the usual amino acid content. The slender rodlets predominate, though occasional droplets are present (Cf. fig. 1). Objective  $0.25 \lambda 0.14 \text{ A}-$ .

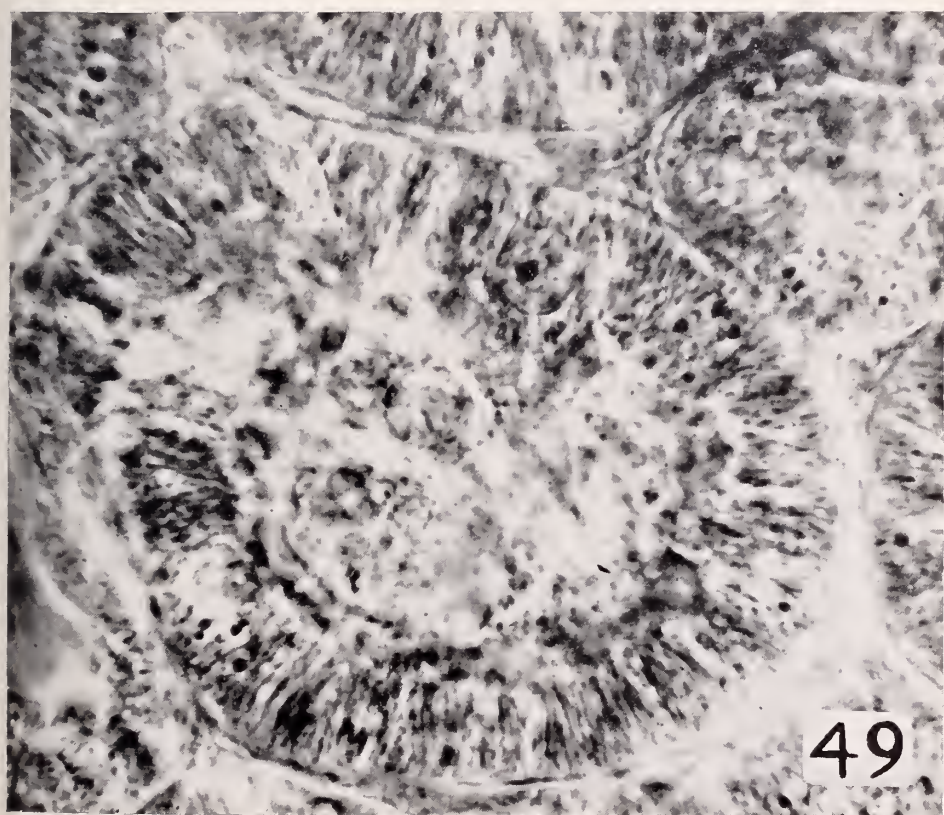


FIG. 50 to 57. Similar unstained frozen sections of formalin fixed proximal convolutions of rats on various amino acid regimens.

FIG. 50. *dl*-isoleucine. "Bright phase" contrast showing bright and dark droplets filling the tubule cells. Objective  $0.25 \lambda$  0.14 A+.

FIG. 51. The same tubule under "dark phase" contrast. The inverse picture, but there are more "dark" droplets in the former than there are "bright" in the latter. Objective  $0.25 \lambda$  0.14 A-.



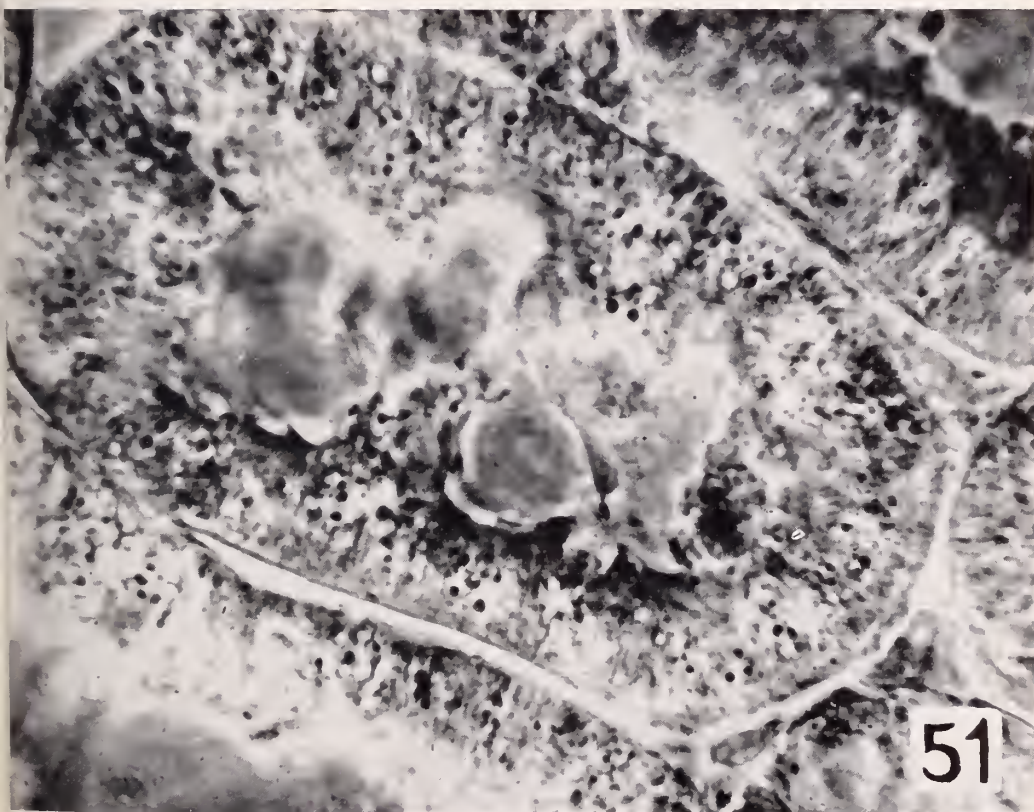
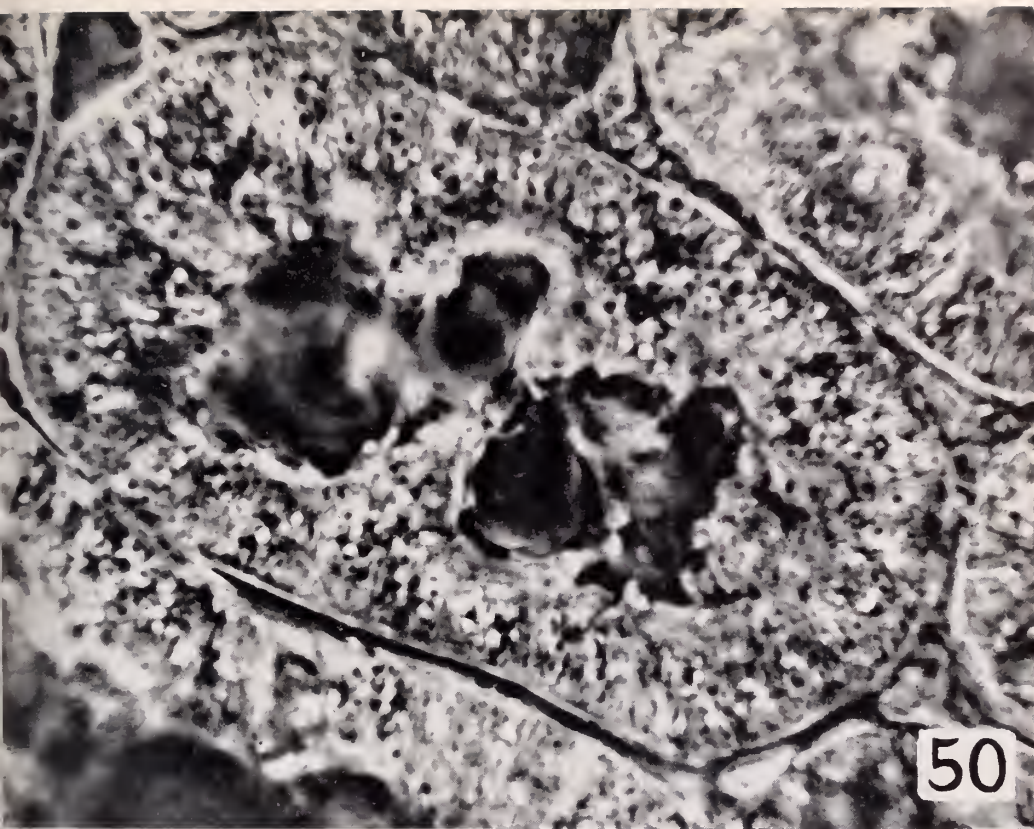




FIG. 52. *l*(-)-leucine. "Dark phase" contrast of a proximal convolution filled with dark droplets and only a few rods. Objective  $0.25 \lambda 0.14 \text{ A-}$ .

FIG. 53. The same convolution under "bright phase" examination. Objective  $0.25 \lambda 0.14 \text{ A+}$ .

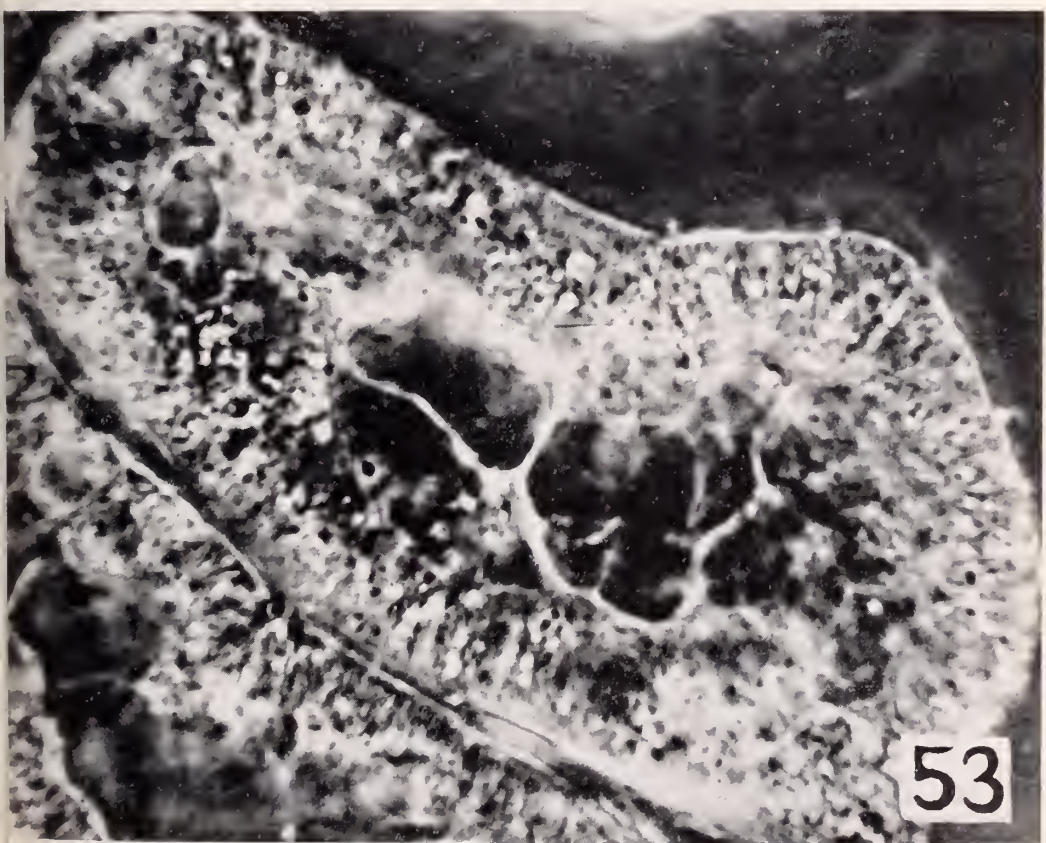


FIG. 54. The same convolution under another type of "dark phase" contrast. The relative sparsity of droplets is due to the fact not all that appeared in the previous two figures are visible. The significance of these optical differences in terms of chemical constitution is not known. Objective  $0.25 \lambda 3.0 \text{ B-}$ .

FIG. 55. Glycine. The persisting rodlets are well shown in the upper part of the tubule but the remainder is filled with dark droplets. Objective  $0.25 \lambda 0.14 \text{ A-}$ .



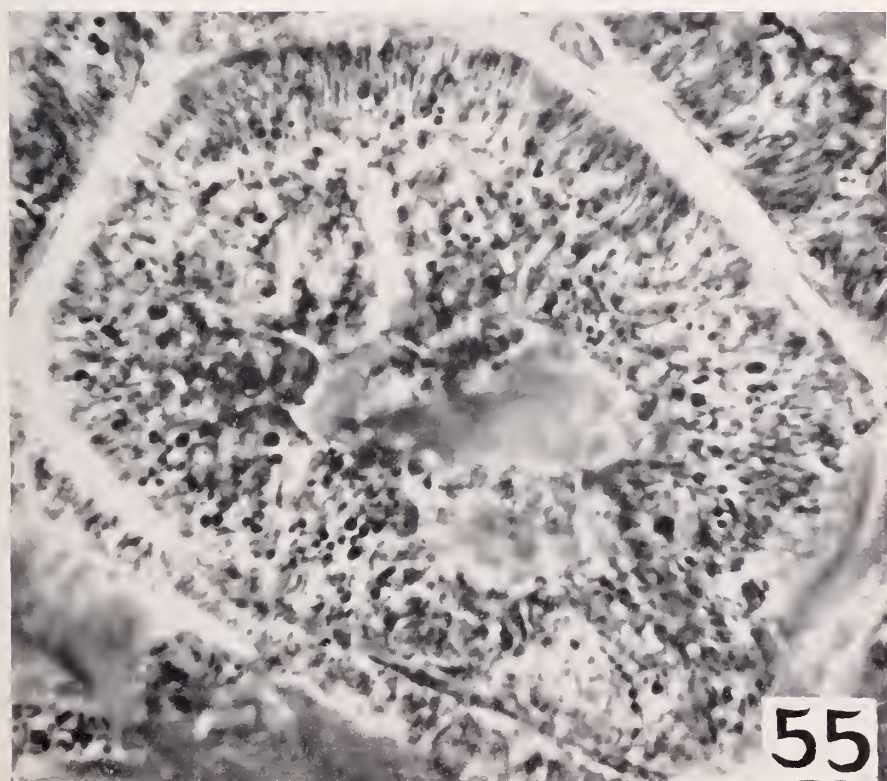
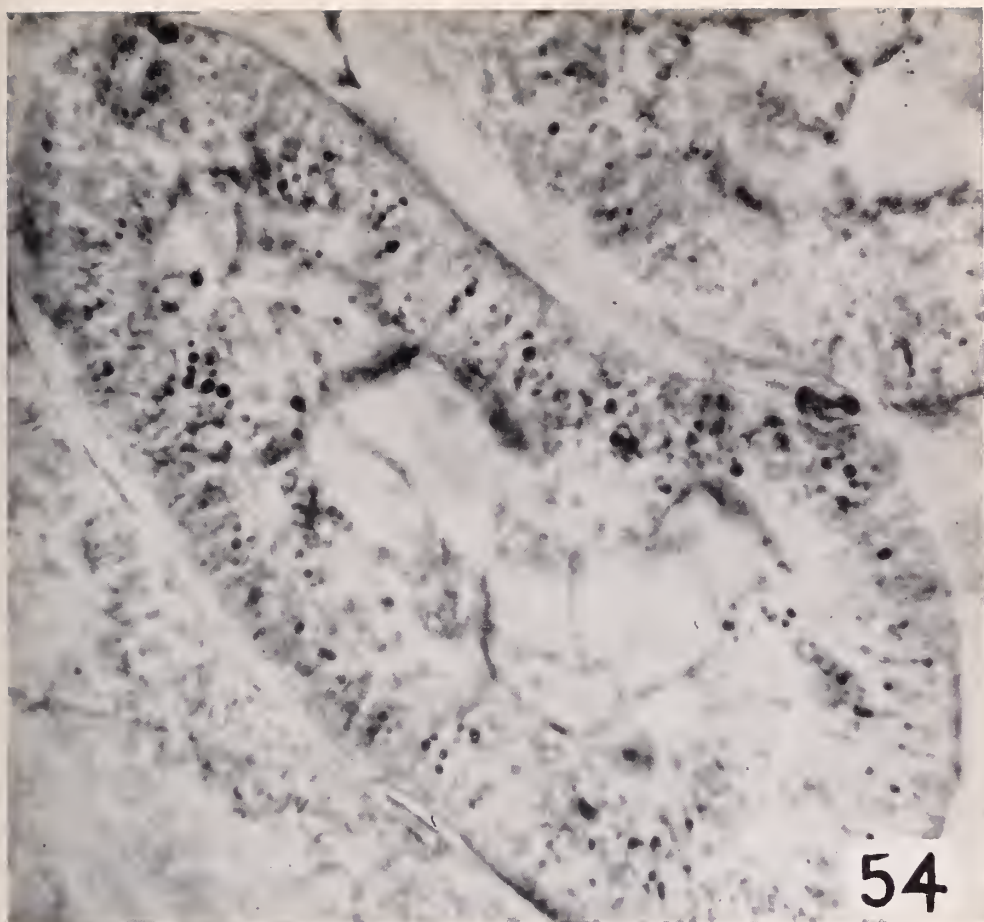




FIG. 56. The same tubule under "bright phase" examination. The rodlets are not so evident as in the preceding photograph. Objective  $0.25 \lambda 0.14$  A+.

FIG. 57. The same tubule under another method of "dark phase" contrast. Rodlets are poorly shown and not all the droplets of the preceding figures are visible. Objective  $0.25 \lambda 3.0$  B-.

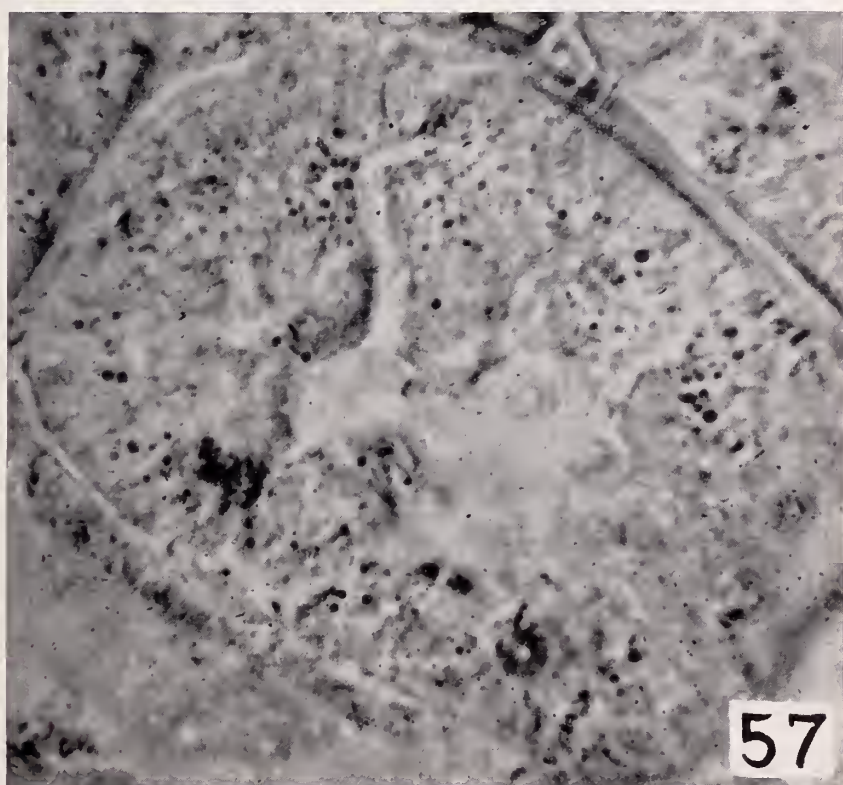
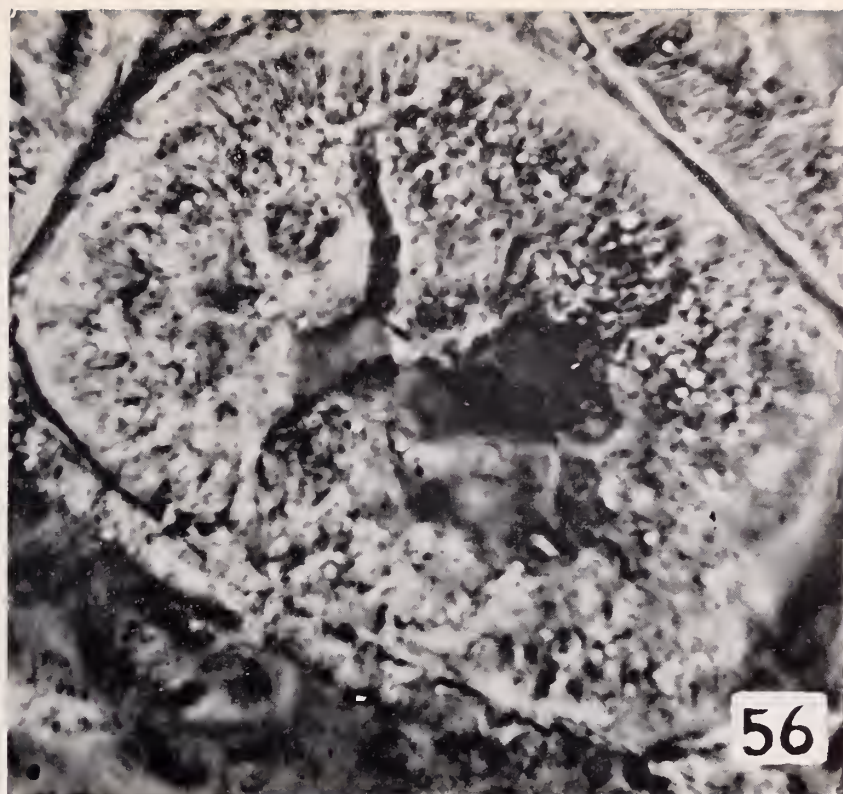


FIG. 58. Reprinted from Oliver and Lund (17). Sections from perfused frogs kidneys whose function and structure were studied by the extra-vital method.

A. Proximal convolution from the kidney which was secreting nothing and which was absorbing only water, sugar and electrolytes. The renal cells show the long filamentous rodlets and no droplets.

B. Proximal convolution from the kidney secreting neutral red. No filamentous mitochondrial rodlets remain and the cells are filled with droplets which in fresh specimens are dark red.

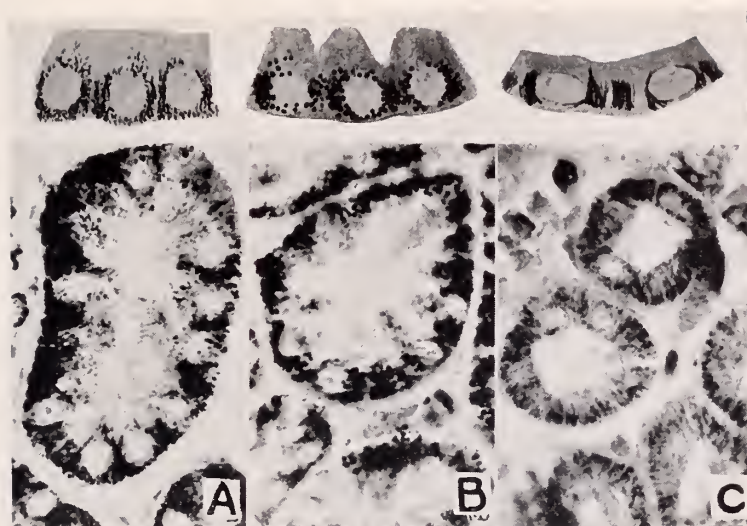
C. The "distal convolution" of the second kidney which was secreting neutral red. As in the mammal, this segment contains no secretion droplets. Zenker fixation and iron hematoxylin stain.

FIG. 59. Reprinted from Oliver and Lund (17). Sections from perfused frogs kidneys whose function and structure were studied by the extra-vital method.

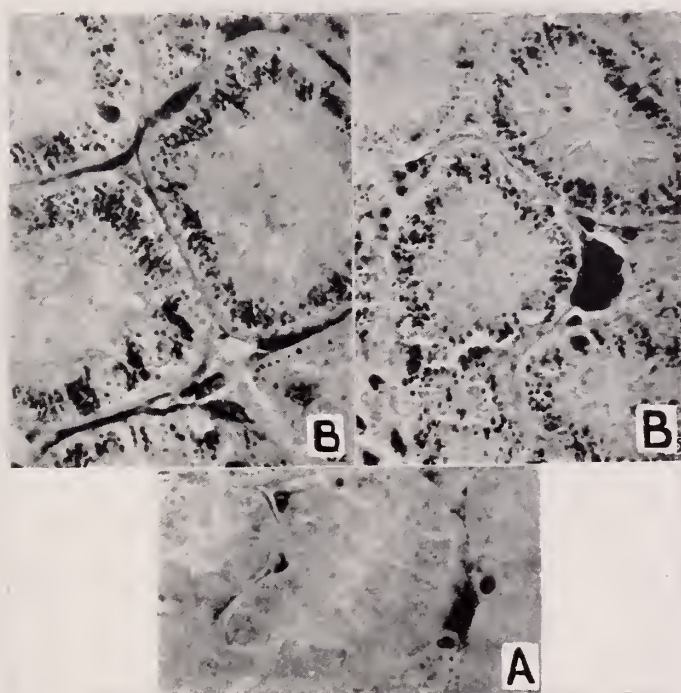
Gram stains of section of the non-secreting and the secreting kidney of the same experiment.

A. In the non-secreting kidney the rods do not stain and there are no droplets.

B. The droplets in the secreting kidney are Gram-positive. Zenker fixation and Gram stain.



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## DUMBBELL TUMORS OF THE SPINE\*

IRA COHEN, M.D.

Dumbbell or hourglass tumors of the spine are so called because of their shape. They are a type of spinal cord tumor that concern chiefly the surgeon. From the viewpoint of diagnosis there is nothing characteristic about them which on neurological signs distinguishes them from other spinal cord tumors. Palpable paraspinal masses and roentgenographic studies will usually supply the evidence which permits the neurological surgeon adequately to plan his operation.

As Jelsma (4) pointed out in his report of an hour glass tumor of the cervical spine, the relatively few cases recorded in the literature is not likely an index of the frequency of such tumors. He cited eighty-nine cases previously reported and added one of his own. In the same year (1941) Eden (3) reported the incidence of 32 dumbbell tumors in a series of 234 spinal cord tumors, extra- and intramedullary. We have had 11 dumbbell tumors recorded in 148 cases of primary spinal cord tumors (Table I).

Dumbbell tumors may lie wholly within the spinal canal. They are then extra- and intradural. The waist of the hourglass corresponds to the site of passage thru the dura. Others are extra- and intraspinal. The waist then usually corresponds to the intervertebral canal, though it may be interlaminar (as in Case 1). The intraspinal portion of this group may be wholly extradural or extra- and intradural. To these three types Eden adds a fourth in which the bulk of the tumor is outside the spine while the intraspinal part is represented by a nubbin projecting into the intervertebral foramen.

Unusual as this latter type is it is important that the general surgeon keep it in mind in operating upon paravertebral tumors. In fact any type of dumbbell tumor, except the wholly intraspinal variety, may, because of a paravertebral mass and absence of outstanding complaints referable to the spinal cord, come under the care of a general surgeon. Thus Case 10 in this series had had a biopsy of the mass in the neck before coming under our observation. Another probable instance was observed when I was asked to see a patient who had developed a flaccid paraplegia immediately following the removal of a mediastinal mass. Because of manometric block an immediate laminectomy was carried out. In the spinal canal there was found one end of a gauze packing which had been placed to control hemorrhage following the removal of the mediastinal tumor.

Of the eleven dumbbell tumors we have operated upon, 7 were in the cervical, 3 in the thoracic and 1 in the lumbar segment of the spinal canal. An unusually large proportion of the tumors, 6, were meningiomas.

In 4 of the meningiomas the laboratory report made use of a modifying phrase. In Case 1 attention was called to the many mitotic figures. In Case 5 the tumor was designated as a cellular type. In Case 2 and Case 3 note was made of the meningioma containing or engulfing ganglion cells.

\* Presented as part of The Mount Sinai Hospital Program of the American College of Surgeons Meeting, September 8, 1947.

*Case 1.* A middle aged woman was operated upon in 1933. She had complaints of pain and progressive weakness for 8 months prior to the operation and had a complete paraplegia at the time of operation. The tumor in the thoracolumbar region was extradural and

TABLE I  
*Character and location of tumors*

	CERVICAL	THORACIC	LUMBAR
Intra- and extradural.....	M N		
Extradural and extraspinal.....	M N	M	
Intra- and extradural and extraspinal.....	M N N	N N	M

M = Meningioma.

N = Neurofibroma.



FIG. 1. Case 2. Narrowing of left half of arch of C 1.

had invaded the muscles of the back. The extension from within the canal was between the laminae. A second operation was done six months later. At the time of the second operation the patient had a flaccid paraplegia. The tumor was found intradural as well as extra-

dural and extraspinal. She survived 6 months. The gross appearance of the tumor was that of a sarcoma. It showed whorls but many mitotic figures and was reported as a meningioma. From its invasive character as well as gross and microscopic appearance this tumor would be classified today as a sarcomatous meningioma.

*Case 2.* H. G. a youth of 17 was observed on the neurological service in 1938 because of headaches and paresthesias of the hands. There were multiple tumors along the course of many nerves and many café-au-lait spots. Both upper extremities were weak. The spinal dynamics showed no block but the total protein was 172 mg. per cent. The report of a biopsy of a mass in the forearm was neurofibroma. He was discharged with the diagnosis of neurofibromatosis and given x-ray therapy. He improved until 1941 when he experienced increasing weakness of both legs and the right arm. He showed a spastic paraplegia, weak-



FIG. 2. Case 2. Enlarged intervertebral foramen noted on second admission.

ness of the arms, hyper-reflexia and bilateral Babinski response. There were posterior column disturbances in the lower extremities but sensation was not otherwise disturbed. The x-ray studies showed a narrowing of the left half of the arch of C 1 (fig. 1).

Cervical laminectomy (Gross) showed that a mass protruded between C 1 and C 2 into the tissues of the neck. The intraspinal portion was extradural. The histology of the excised tumor was pachymeningioma engulfing dorsal ganglion cells.

The patient improved following the operation, the improvement lasting approximately three years. Then the right leg began to lose power and a swelling was noted to the left of the midline in the neck.

Early in 1945 he was admitted for the third time because of pain radiating from the mass in the neck to the occipital region. There was a mass 5 by 3 inches in the left occipito-cervical region. There was evidence of pyramidal tract involvement. X-rays of the spine showed enlarged intervertebral foramina at C 2 and C 3 (fig. 2).



At operation the mass was found adherent to the transverse process, part of it dipped into space between the atlas and the rim of the foramen magnum. The left great occipital nerve was about six times the normal size. The tumor was reported as neuro-sarcoma infiltrating muscle. Pain was relieved by the operation.

Seven months later he was admitted for the fourth time with a history of progressive weakness of extremities and bulbar signs. He died five days later.

There is a similarity of this case to the one reported by Jelsma: a dumbbell tumor showing malignant features in the cervical region of a patient with Von Recklinghausen's disease. The spinal tumor in our case was a meningioma. The simultaneous harboring of meningeal tumors and those springing from nerve elements has been discussed recently by Cushing and Eisenhardt in their book on meningiomas (1) and by Davis in his monograph on primary tumors of the optic nerve (2).

*Case 3.* I. R. a 50 year old man admitted in 1937 had a 6 year history of pains in the right shoulder with occasional tingling sensation down the arm. There was a history of gradually increasing weakness of the right leg. A paraparesis with increased deep reflexes was found. Hypaesthesia was present below thoracic 1. A manometric block and total protein of 200 mg. per cent was noted. The tumor which extended from C 5 to T 1 was both extra- and intradural. It was reported as a meningioma containing ganglion cells (the laminectomy was done by Dr. Kaplan). For the 6 years that the patient reported after the operation he was self supporting, but had some residual weakness in the left arm.

*Case 4.* A. P. a 23 year old woman dated her complaints to a time 6 weeks prior to the birth of her child. The first symptom was that of tingling sensation in the arm which in the year prior to her admission to the hospital progressed to involve both arms and both legs with motor and sensory loss. Her spinal fluid studies showed a partial block and elevated total protein. The x-ray examination showed absorption of the left pedicles of C 6 and C 7 (fig. 3). At operation an extradural tumor was found to extend from C 4 to C 7 vertebra and to project through the intervertebral foramen with the 6th cervical root. The intradural portion was not recognized at first. When the dura was opened a tumor about 2 cm. by 2 cm. was exposed. In addition the inner side of the dura presented a shaggy appearance. To remove all tumor tissue the dura had to be sacrificed and replaced by a facial graft. The tumor was reported as a meningioma.

Had the possibility of an intradural extension not been recognized it would have been missed and allowed to remain.

*Case 5.* A. R. a 22 year old woman had a sudden onset of numbness of all toes 8 months prior to her operation. The numbness was followed by loss of position sense and then loss of power. She had a spastic paraparesis when she was seen. Her spinal fluid showed a complete block and elevated total protein. Laminectomy disclosed an extradural tumor which extended through the 10th intervertebral foramen into the tissues of the back lying on the pleura. It was reported as a cellular meningioma.

*Case 6.* F. K. a 40 year old man had "sprained" his back 5 years prior to the onset of the present complaints. He noted numbness of the left thigh which began above the knee and spread upwards. This was followed by pain in the same location, with radiation into the lower leg. His symptoms were aggravated by rest in bed. He had been treated by "stretching" though the total protein was reported to be 170. There was some weakness of the entire left lower extremity, absent ankle jerks and left knee jerk. There was questionable diminution of touch over the outer side of the left thigh, leg and foot. The x-ray films showed an absence of the pedicle of L 3 and a pressure indentation of the posterior aspect of the body (fig. 4). An intradural tumor which projected in part through the 3rd lumbar intervertebral foramen was removed. It was reported leptomeningioma with old and recent hemorrhages and necrosis.

This was the only lumbar dumbbell tumor encountered in the series. Prior to admission to the hospital it had been considered a protruded intervertebral disc though the x-ray films promptly suggested the correct diagnosis.

Turning now to the neurofibromas all but one were in the cervical region.

*Case 7.* I. S. a 47 year old man first noted some numbness of both feet four and a half years prior to entering the hospital. About 3 years later he first experienced muscle cramps

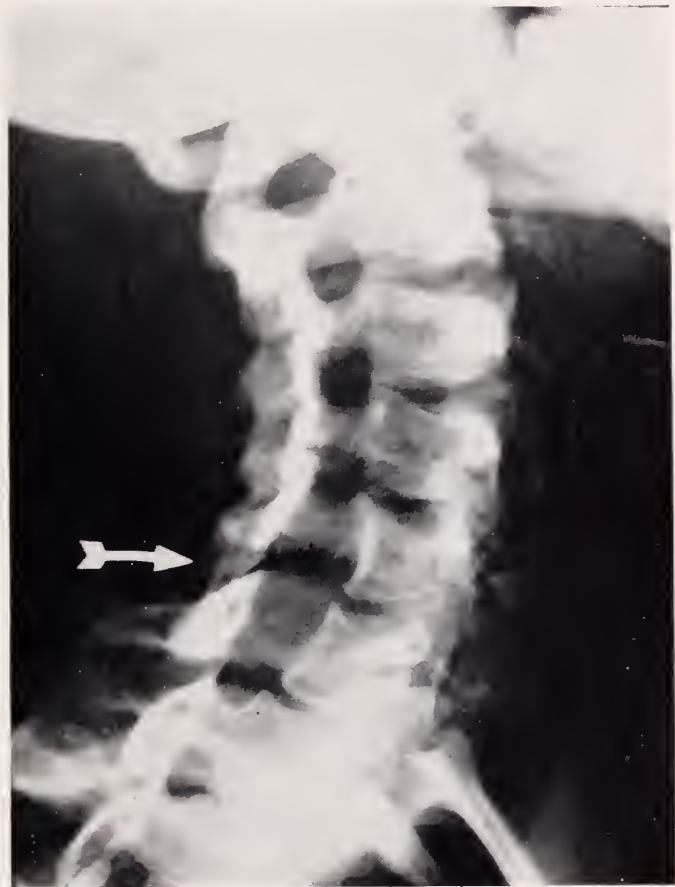


FIG. 3. Case 4. Oblique view showing bone absorption at C 6 and C 7.

in the legs which gradually increased in severity and frequency. The examination showed tonic spasms of the muscles of the right lower extremity, depressed deep reflexes, bilateral Babinski response with a sensory level at the 10th thoracic dermatome. There was a spinal fluid block. The x-ray film (fig. 5) showed changes in the 8th and 9th thoracic vertebra and a circular mediastinal mass at this level. At operation this mass was found to be continuous with a small intra-arachnoid tumor. The latter was removed and reported a neurofibroma. The mediastinal mass was removed by the thoracic surgeons at a later date.

There are times when in the presence of a tumor such as was found in this patient, arrangements can be made with the thoracic surgeons for the removal

of both the intraspinal and the mediastinal portions in one step. Such a procedure was described by Harrington and Craig (5). Should this be considered inadvisable it is well to remove the intraspinal portion first. This order of operating also applies to dumbbell tumors in the cervical and lumbar regions.



FIG. 4. Case 6. Bone absorption of both arch and body at L 3.

Such a procedure allows freedom in the manipulation of the extraspinal mass, which would not obtain were the intraspinal portion still attached.

*Case 8.* L. K. a 20 year old boy began to have pain and numbness in the right hand about a year prior to entering the hospital. These symptoms increased and they involved the entire arm. Pain extended to the shoulder and neck. Later numbness of the trunk and the toes on the right were noted. This was followed by weakness of the right arm and leg.

The examination disclosed a Brown-Sequard picture, the motor side on the right. The upper sensory level was not clear. There was no block of the spinal fluid which showed normal chemistry. The x-ray films showed a destruction of the lamina of C 5 on the right and some involvement of the vertebral body.

At operation an extra-intra-dural tumor was removed. A complete closure of the dura was not obtained. On the tenth post-operative day there was a spinal fluid leak for a day. Then for 6 weeks fluid accumulated in the tissues of the neck and there was spiking fever without any apparent cause. This cleared up spontaneously.

In spite of the daily rise in temperature the patient's appearance and feeling was that of well being. This is the clinical picture encountered occasionally following a suboccipital craniotomy, most frequently, though not always associated with a collection of spinal fluid in the soft tissues.

*Case 9.* H. N. a 49 year old woman, who was known to have hyperthyroidism, had complained of numbness of the hands and feet for a year. Her gait became unsteady. There

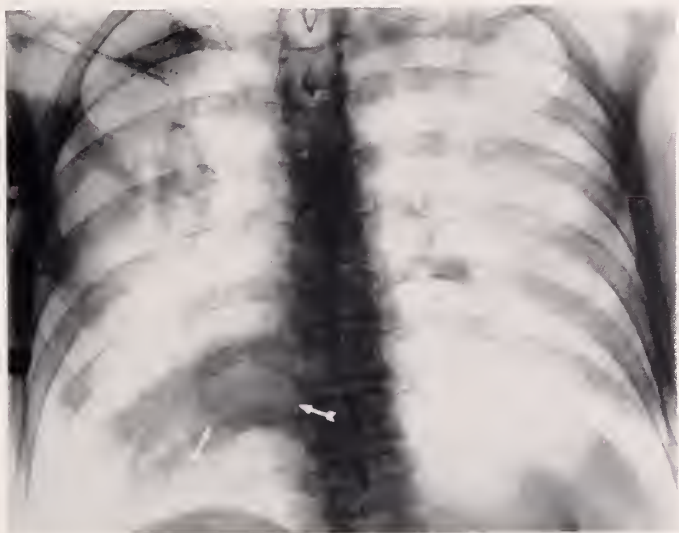


FIG. 5. Case 7. Mediastinal Mass—The vertebral changes do not show.

was ataxia in all four extremities, position sense was absent in the fingers and toes. Pain and touch were impaired in the right arm. There was a spinal fluid block and elevated protein. The basal metabolism was plus 26. At operation a dumbbell tumor was found projecting through the 6th intervertebral foramen. The intraspinal part was inside the dura and larger than the extraspinal portion. From the fourth to the fifteenth week the patient ran a spiking fever which was never explained, the search going so far as to reopen the wound. The tumor was a neurofibroma.

The fever in this case resembled that in Case 8 but was of longer duration. The dura was left partly open as it had been in that case. We have been unable to produce a febrile reaction by the subcutaneous or deep injection of a patient's own spinal fluid.

*Case 10.* C. H. a 53 year old woman had had a biopsy, reported as neurofibroma, of a tumor of the right side of her neck. She had noticed the tumor for about 5 months, but for 2 years she had complained of pain radiating down the right arm and stiffness of the fingers.



The arm had become very weak and there was weakness of the right leg. The reflexes in the upper extremities were depressed, in the lowers they were exaggerated and there was a bilateral Babinski response. The mass in the neck was about 6 cm. in diameter and situated



FIG. 6. Case 10. Extensive bone destruction C 4, 5 and 6.

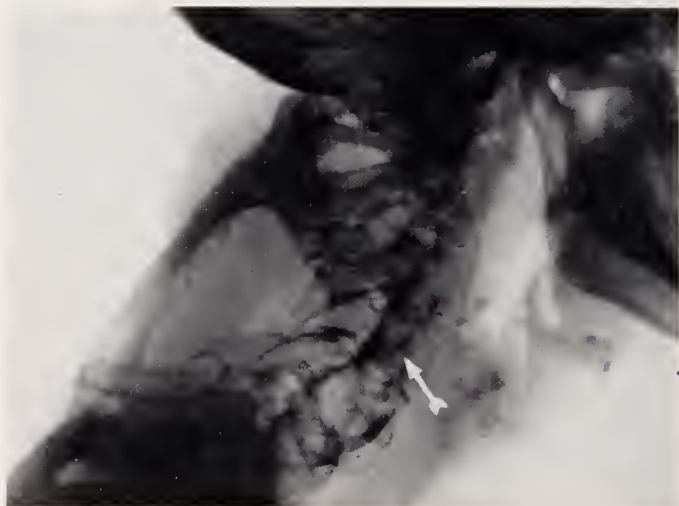


FIG. 7. Case 10. Three years following operation. Bone graft in situ and some bone replacement.

in the posterior triangle. There was a partial block and a total protein of 160 in the spinal fluid. There was extensive bone destruction of the 4th, 5th and 6th cervical vertebrae (fig. 6). The destruction was such that it was considered prudent to have the neck immobilized in a cast and to operate through a window in the cast. A hemi-laminectomy was done. The tumor was found extra- and intradural as well as intra- and extravertebral. After the

tumor was removed a bone graft was inserted (Dr. Haas). X-ray films taken 3 years later (fig. 7) illustrate this graft *in situ* and show some replacement of bone.

*Case 11.* M. M. a 36 year old woman had complained of numbness in the right hand and arm for a year. About 8 months later the right leg became weak. She showed pyramidal tract involvement of all four extremities with hyperactive deep reflexes. Sensory changes were not constant. At times there was noted loss of vibratory sensation in both lower ex-



FIG. 8. Case 11. Bone absorption in cervical spine as shown by arrows.

tr extremities and the right upper extremity. Pain sense was lost at times from C 4 to T 10 and diminished below this. The spinal fluid showed no block and normal chemistry. After injection some lipiodol remained in the system. Changes in the x-ray films were first noted after the tumor had been removed (fig. 8).

On two occasions in the operating room the patient went into profound shock before an anaesthetic was given. On the third attempt an extra-spinal and an extra-dural tumor was exposed extending anteriorly opposite C 2. The dura was opened and the cord seen pushed backward by the tumor. In order to gain additional room part of the occiput and arch of the atlas were removed. In doing this a hemorrhage took place that could only be controlled by packing. At a second stage a week later the tumor was completely removed. The intra-

spinal part proved to be entirely extradural. The anterior portion elevated the anterior dura. This tumor was reported Schwannoma.

In the diagnosis of dumbbell tumors the most important single aid is the x-ray examination. Views of the intervertebral foramina will show enlargement of the foramen in those cases in which the waist of the tumor lies in or extends through the foramen. Should the tumor escape from the canal between the laminae there will be erosion of the bones at this site. In addition to the changes in the bones of the spine further evidence may be furnished by a paravertebral soft tissue mass. This is most striking in those tumors which extend into the mediastinum (fig. 5). In those tumors which lie completely within the spinal canal and whose hour glass designation is based on the waist connecting the intra- and extradural portions there may be no x-ray evidence or only that evidence which may be observed in any spinal cord tumor which is not peculiar to the group under discussion.

The larger paravertebral extensions are usually to be found in tumors of nerve root origin rather than those from the meninges. Case 1 is an exception to this observation but here the question of malignancy arises.

The operative removal is planned to meet the individual case. In general the intraspinal portion is removed first. In some instances a two stage operation is planned from the onset. In other cases such a procedure may be forced upon the surgeon in the course of the operation. Where an extensive intrathoracic operation is needed the thoracic surgeon may be present at the primary operation or take over at a second stage.

#### SUMMARY

1. Eleven cases of dumbbell tumors of the spine have been described.
2. The importance of the preoperative diagnosis of these is discussed.
3. The diagnostic aid given by roentgen studies is pointed out.

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# THE TREATMENT OF HYPERTENSION BY ACCELERATED SODIUM DEPLETION<sup>1</sup>

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The importance of restricting salt intake in hypertension has been stressed in the past, particularly by Allen and Volhard (1, 2, 3). More precise clinical and experimental investigations conducted in recent years indicate that the depressor effect of salt depletion is related to the curtailed intake of sodium (4, 5, 6, 7, 8, 9). The relationship implies that the fall in blood pressure resulting from a restricted intake of sodium could be accelerated by increasing the rate of sodium excretion. This report details certain observations on eight hypertensive patients who were subjected to rapid sodium depletion by restricting the dietary intake of sodium to 200 mg. and simultaneously increasing the rate of urinary sodium excretion by means of mercurial diuretics.

## METHODS

The patients were first maintained on the regular ward diet for periods of two to three weeks. During this time the blood pressure, the weight and the fluid balance were recorded daily; electrocardiograms and teleoroentgenograms were obtained; and renal function was measured by urea clearance, by excretion of phenolsulfonphthalein, and by concentration tests. The urea nitrogen, chloride and carbon dioxide content of the blood were determined. The condition of the smaller blood vessels was evaluated micropylethysmographically following the administration of nitroglycerine, dihydroergocornine (DHO),<sup>4</sup> and tetraethylammonium chloride (TEAC).<sup>5</sup> Retinal changes were appraised by an ophthalmologist. In three patients the red cell, plasma and total circulating volume were computed by the dye method after the injection of T 1824. The preliminary control period of observation was continued until the diastolic pressure remained constant within 10 mm. of mercury over a period of four consecutive days.

The patients were then given a diet composed of 75 Gm. of protein, 90 Gm. of fat, 240 Gm. of carbohydrate, and a maximum of 200 mg. of sodium. After five to seven days on this diet, injections of mercupurin were added to the regimen. This drug was given intramuscularly in doses of 2 cc. at intervals of one to four days. The number and frequency of injections were governed by the level of the blood urea nitrogen, by the subjective symptoms and by the changes in blood pressure. The total quantity of mercupurin administered to each patient varied, ranging from a minimum of 8 cc. in one patient to a maximum of 32 cc. in another. During the interval of forced sodium diuresis the clinical and laboratory procedures performed during the control period were repeated. The benefits of rapid sodium depletion were judged by the magnitude of the reduction in blood pressure, by the improvement of the retinal abnormalities, by the disappearance of symptoms, by the increase in vascular lability as determined from the micropylethysmogram, and by the time

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elapsing before any of these changes might become apparent. All the patients with the exception of one were ambulatory during their period of hospitalization.

The severity of hypertension was classified on the basis of height of diastolic pressure, extent of retinopathy, degree of cardiac enlargement, existence of electrocardiographic abnormalities, and the presence of reduced kidney function. By these criteria the hypertension was considered to be "moderate" in one patient, "severe" in three patients, and "malignant" in the remaining four patients.

## RESULTS

1. *Effects upon blood pressure.* Five of the eight patients, including two who had malignant hypertension, developed a significant fall in blood pressure following the administration of mercuripurin. The decline in the level of the arterial pressure first became apparent on an average of 4.5 days after the inception of mercurial injections. A sixth patient with malignant hypertension exhibited an appreciable decline in pressure after four injections of mercuripurin administered at intervals of 2 days, but because of a rise in the level of blood urea nitrogen the drug was discontinued. One week thereafter the blood pressure had returned to its previous levels.

The amount of mercuripurin required to induce the maximal attainable reduction in blood pressure by forced sodium diuresis varied widely in the five patients. Thus, one subject needed but three injections administered over a period of four days while another received twelve injections over a period of seventeen days before normotensive levels were reached. On an average, four injections of the drug were required to elicit the first appreciable fall in pressure and an additional two injections were needed to attain the maximal depressor effect.

The composite blood pressures before and after the inception of mercuripurin therapy are listed in the table. The actual reductions in blood pressure are appreciably greater than are indicated by the composite values since these incorporate all the sphygmomanometric determinations following the first injection of mercuripurin and thus fail to correct for the factor of time lag. The foregoing is more clearly exemplified by Case 8 which illustrates the magnitude and rapidity of the reduction in blood pressure which may be attained by rapid sodium depletion (fig. 1). This patient had an initial blood pressure of 244 systolic and 124 diastolic. Eight days after the onset of treatment and after six injections of mercuripurin the blood pressure fell to 126 systolic and 84 diastolic.

Four of the five patients who attained significant reductions in the levels of the arterial blood pressure by accelerated sodium depletion have now been followed for periods up to six months since discharge from the hospital. In each instance the blood pressure has been maintained at these reduced levels by simple adherence to the 200 mg. sodium diet.

2. *Effects upon the microplethysmogram.* It has been demonstrated that the existence of vasospasm may be determined in hypertensive patients by measuring the volume pulse amplitude and the blood flow in both great toes before and after the administration of nitroglycerine, DHO and TEAC with a specially designed direct writing photoelectric microplethysmograph (10). By employing a modification of this procedure it was found that the results of thoracolumbar sympathectomy were prognosticated correctly in 27 out of 30 hypertensive subjects. Of even more significance was the fact that the seven patients of this series who failed to reveal any vasospastic component plethysmographically failed to develop a reduction in blood pressure after sympathectomy (11).

Microplethysmograms were obtained on all patients in the present study during the control period. In four no significant plethysmographic alterations followed the attempted release of vasomotor tone. These patients were restudied with the microplethysmograph after rapid sodium depletion. At this time it was found that three of the four now had a marked increase in both the blood flow and volume pulse amplitude in response to the administration of TEAC. The development of vascular lability as evidenced microplethysmographically after sodium depletion was accompanied by a significant reduction in blood pressure in two of these three patients. When it is recalled that sympathectomy

TABLE 1  
*Composite table presenting the essential laboratory and clinical findings in the eight patients before and after accelerated sodium depletion*

SEX	AGE	SEVERITY OF HYPERTENSION	COMPOSITE BLOOD PRESSURE		BLOOD PRESSURE	HYPERTENSIVE RETINOPATHY		MICROPLETHYSMOGRAM BEFORE KX	MICROPLETHYSMOGRAM AFTER KX	HEADACHE BEFORE KX	HEADACHE AFTER KX
			Before Rx	After Rx		Before Rx	After Rx				
F	23	Malignant	250/150	250/140	242/142	Grade IV	Grade I	Poor response	Good response	Grade IV	Grade 0
F	48	Severe	228/136	175/109	160/90	Grade III	Grade I	Poor response	Good response	Grade 0	Grade 0
F	60	Moderate	227/112	160/90	128/76	Grade II	Grade I	Good response	Not repeated	Grade 0	Grade 0
F	50	Malignant	242/132	202/102	190/92	Grade IV	Grade II	Good response	Increased response	Grade IV	Grade 0
F	55	Severe	256/148	248/140	240/136	Grade III	Grade I	Good response	Increased response	Grade IV	Grade 0
M	33	Malignant	240/159	208/137	200/120	Grade IV 20/200 + diop- ters papille- dema	Grade III 20/70 I diopter papilledema	Poor response	Good response	Grade IV	Grade 0
M	48	Malignant	252/154	225/140	225/140	Grade IV	Grade IV	Poor response	Unchanged	Grade IV	Grade II
F	46	Severe	208/115	143/97	126/84	Grade III	Grade I	Good response	Not repeated	Grade IV	Grade 0

has proven ineffective in those hypertensive patients failing to exhibit vasospasm, this observation assumes clinical importance since it implies that certain of these patients may nevertheless be benefited by accelerated sodium depletion. It also raises the question as to whether the therapeutic potentialities of splanchnicectomy could not be increased by a preliminary period of "desalting."

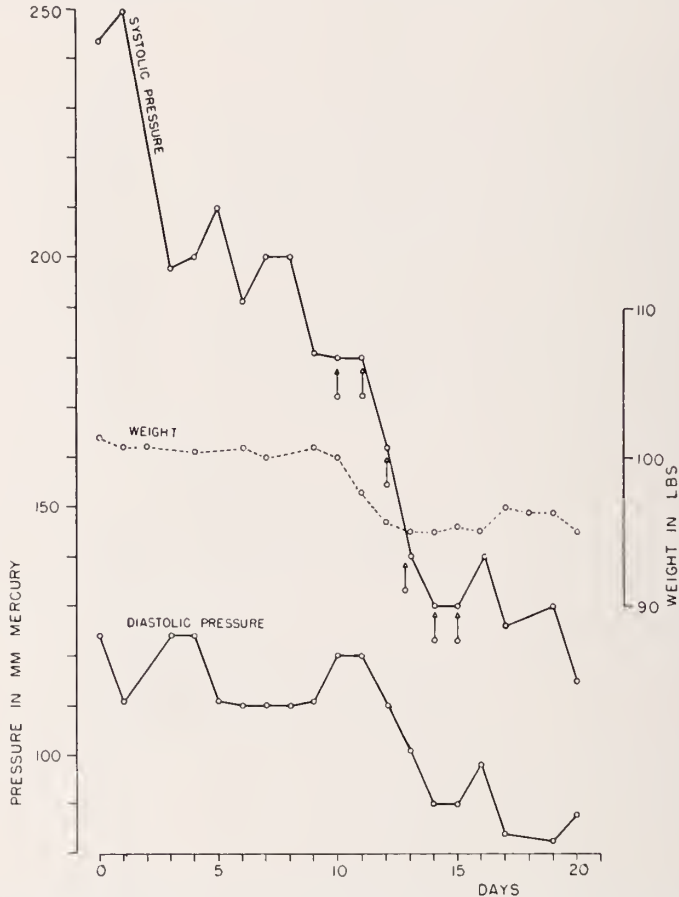


FIG. 1. Note the pronounced and rapid decline of systolic and diastolic pressure following accelerated sodium depletion. The 200 mg. sodium diet was begun on the seventh day. Arrows indicate days when mercupurin was administered.

In two additional patients in whom a pronounced increase in peripheral blood flow followed the administration of TEAC during the control period, vasolability was further increased after sodium depletion.

During the preliminary period of control TEAC induced a profound but temporary fall in blood pressure in four of the eight patients. The four who failed to develop a significant decline in pressure after TEAC were the same patients who showed no plethysmographic evidence of vasospasm before salt depletion. After accelerated sodium diuresis the injection of TEAC was followed by a transient reduction in blood pressure to normotensive levels in three of these four patients. These were the same subjects in whom salt depletion therapy was followed by plethysmographic evidence of vascular improvement. This reversal of otherwise fixed vascular patterns is especially important since it implies that the

progress of arterial disease in hypertension may be halted or retarded by this form of therapy.

3. *Effects upon retinopathy.* The grade of hypertensive retinopathy in each patient is listed in the table and is based upon the classification of Wagener and Keith (12). It was found that the retinal abnormalities regressed markedly in five patients, slightly in two patients, and remained unchanged in one patient while on the accelerated sodium depletion regime. Improvement in the fundi were detectable within an average of fifteen days after the initial injection of mercurpurin. It is interesting to note that in two patients the severity of the retinopathy waned despite the fact that the general level of blood pressure remained unchanged. In this respect the retinal improvement paralleled the plethysmographic rather than the blood pressure alterations.

4. *Effects upon symptoms.* Six patients complained of intractable headache upon admission to the hospital. Three of these patients exhibited the symptom complex of "malignant" hypertension. Five of the patients, including two with malignant hypertension, attained complete relief after accelerated sodium depletion. The sixth patient experienced partial improvement as manifested by a significant decrease in the frequency and severity of headache. Disappearance of this complaint was noted on an average of nine days after the first injection of mercurpurin.

Four patients complained of marked weakness upon entry. As with headache this symptom disappeared rapidly after sodium depletion.

Three patients developed a rise in the level of blood urea nitrogen during the period of mercurpurin administration. In two the rise was slight and disappeared spontaneously. In the third patient the elevation was of sufficient magnitude to warrant discontinuation of further mercurial therapy in spite of the fact that the azotemia appeared to be related to hemoconcentration following the renal deviation of water rather than to true renal excretory insufficiency.

In three patients the improvement in symptoms was accompanied by a reduction in the size of the heart and by a regression of the electrocardiographic abnormalities.

#### COMMENTS

Therapeutic failures with the Kempner regimen result chiefly from a refusal of patients to maintain the rigid diet for requisite periods of time. The diet is unpalatable and the beneficial effects usually appear only after eight or more weeks. Our experience indicates that the rate of improvement may be accelerated materially by increasing the depletion of body sodium with mercurial diuretics. Furthermore the objections to dietary management may also be circumvented by use of a more palatable diet than that of Kempner. Our diet, the composition of which has been described previously, is balanced metabolically, is simple to maintain and imposes no undue psychic hardships.

The relative merits of the Kempner and accelerated sodium depletion regimens may perhaps be adduced from certain observations made on Case 4. This patient was placed on the standard Kempner diet. After two months the patient improved markedly, as manifested by a decline in blood pressure, disappearance of headache, decrease in heart size and improvement in fundi. Despite the obvious therapeutic benefits the patient complained bitterly about her food. The diet was then changed only by the addition of 8 Gm. of salt a day. Within seven days the blood pressure rose to its former levels and severe headache reappeared. Rapid sodium depletion, by means of our 200 mg. sodium diet and mercurial injections, was then instituted. After eight days headache disappeared and the blood pressure fell. Significantly the pressure now declined to lower



levels than were attained by treatment with the "rice diet." Observations such as these also correlate the rate of clinical improvement with the rate of sodium depletion and lend further support to the contention that sodium depletion is the primary factor responsible for the reduction in blood pressure by dietary means.

We have alluded to the fact that after accelerated sodium depletion certain of the patients developed a marked increase in both blood flow and pulse volume after the administration of TEAC irrespective of the general level of blood pressure, and that such plethysmographic alterations were mirrored by improvement in the fundi. Inasmuch as previous studies have demonstrated that the plethysmographic response to TEAC in an individual is relatively constant under the same conditions of temperature and humidity (13), the observations imply that sodium depletion is capable of inducing a reversal of fundamental functional and anatomical changes in the blood vessels themselves. The fact that such alterations develop even when the blood pressure remains at unchanged hypertensive levels is evidence that at least two independent mechanisms are responsible for the hypertensive syndrome; one which maintains the blood pressure at elevated levels, and another which induces the vascular lesions. In order to elucidate the fundamental relationship between sodium depletion, the reduction in systemic arterial pressure and the anatomical alterations in blood vessels of certain hypertensive patients, we are now studying the urinary excretion of sodium and of certain of the corticosteroid hormones as well as renal clearance and the renal blood flow. The results of these investigations will be published shortly.

#### SUMMARY AND CONCLUSIONS

1. Accelerated depletion of body sodium was induced by restricting the daily intake of sodium to 200 mg. and by increasing the rate of sodium excretion in the urine with mercupurin. The effects of this dual regimen were evaluated in eight hypertensive patients.

2. Five of the eight patients developed a significant fall in blood pressure during their period of hospitalization. Four of these five patients have been followed for periods up to six months since discharge. In each instance blood pressure has been maintained at reduced levels by adherence to the 200 mg. sodium diet.

3. Appreciable lowering in the general level of the systemic arterial pressure was first noted on an average of 4.5 days after the initial injection of mercupurin.

4. It was found that an average of four injections of mercupurin were necessary to induce the initial decline and that an average of two additional injections were required to induce the maximal decline in blood pressure.

5. The combination of forced sodium diuresis and low sodium intake was followed by a pronounced increase in vasolability as measured plethysmographically in five out of six patients. These plethysmographic changes were accompanied by concordant increases in the depressor response to tetraethylammonium.

6. Regression of retinal abnormalities was noted in all but one of the patients. The retinal improvement accompanied the plethysmographic alterations and occurred even when the blood pressure remained unchanged.

7. Six patients complained of headache primarily. This symptom disappeared in five patients; in the sixth it was alleviated considerably following accelerated sodium depletion.

8. The results support the theory that sodium depletion and its associated metabolic phenomena is the primary factor responsible for the reduction of elevated blood pressure by the use of the Kempner and other low salt diets.

9. The observations appear to indicate that the vascular alterations, demonstrated plethysmographically and ophthalmologically, and the elevations of blood pressure occurring in certain hypertensive patients are mediated through somewhat different mechanisms.

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# RESUSCITATION IN THE OPERATING ROOM

## REPORT OF TWO CASES

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Sudden cessation of cardio-respiratory functions in the patient subjected to an operation presents a problem that taxes the resourcefulness of the operating room personnel, especially the anesthetist. Many times it may not be possible to obtain a favorable result, but it must be conceded that some of the deaths are preventable. The literature is replete with numerous reports of successful resuscitations after long periods of suspended cardiac and respiratory activity. Absolute death may not necessarily be simultaneous with respiratory arrest and cardiac standstill (1). In large clinics where all types of operations are performed, there are always a few deaths on the operating table as a result of acute cardio-respiratory failure. Although the exact number has never been recorded, Mautz (2) has postulated the ratio of one sudden death to each 3000-5000 operations. Some believe this estimate is too low.

The two obstacles to be surmounted before normal activity is restored are respiratory arrest and cardiovascular collapse. Respiration and circulation are dependent upon each other. Cessation of one must inevitably adversely affect the other. Therefore all attempts at restoration of function must include simultaneous efforts directed toward both. Cessation of respiration quickly leads to asphyxia. If the asphyxia is permitted to persist paralysis of the vital centers ensues. Artificial respiration must be instituted promptly if a fatality is to be avoided. "A favorable outcome indicates not a miracle but the application of sound therapeutic measures" (3). In many instances, patients may survive relatively long bouts of oxygen want (especially if incomplete), though it has been shown experimentally that the brain cells undergo irreparable damage after eight minutes of complete anoxia. It is of the utmost importance that resuscitative attempts be instituted at once. The earlier the attempt is made the better the prospect of success.

The manual methods of artificial respiration are often impractical for operating room use (4). Since the introduction of the bellows by John Hunter in 1788, many mechanical appliances have been devised which employ the pressure and suction principle for artificial respiration. Because of their unphysiological action, they are rapidly being discarded. The use of the Drinker and Emerson resuscitators, which require placing the patient's body in a chamber, are unfortunately rarely applicable to operating room emergencies.

Branower (4) devised a mechanical respirator which permits rhythmic insufflation of the lungs with oxygen, guarding against excessive pulmonic pressure by means of an adjustable regulator. Recently Crafoord<sup>2</sup> of Sweden described an apparatus called the Spiropulsator. This machine serves a dual purpose. It

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may be used for the administration of anesthesia, but can be transformed in a few seconds into a resuscitator which automatically takes over the function of respiration. This device is designed on physiological principles, and is highly recommended by those who have seen it in operation.

Artificial respiration by intermittent insufflation of the lungs was first introduced by Meltzer (5), but was further developed by Flagg (6) and others to include the introduction of a tube into the trachea under direct laryngoscopy. Through the tube oxygen may be insufflated intermittently. Simple mouth-to-mouth breathing incorporates the same principle of insufflation without mechanical means. When performed properly, it is an efficient and effective method of inflating the lungs, and rarely produces overdistention of the lungs. Mouth-to-mouth insufflation is easily employed, always available, and has often served as a means to eliminate fatal delay. This is exemplified by the cases herein reported.

Many successful efforts to revive the asystolic heart have been reported. Circulatory collapse may precede respiratory arrest; or the heart may continue to function for a short time after respirations cease. Although ordinary methods of palpation and auscultation may fail to reveal a pulse or blood pressure, feeble cardiac action may still be present. Intracardiac injection therapy has been effective in many instances. The important factor is not the particular drug employed, but rather the needle prick of the myocardium, which produces an action current of injury (7), and sets up an electrical potential different from that of the normal pacemaker. If applied soon after the heart has stopped, when the irritability of the myocardium is increased, insertion of the needle may initiate an ectopic beat. This one beat may be sufficient to expel the blood from the left ventricle, supply fresh blood to the coronary circulation, and stimulate normal automatic heart action.

However, the most consistent and successful method of reviving the asystolic heart is by direct cardiac massage. This maneuver has been successful when all other methods have failed. The chief obstacle to its immediate performance is the reluctance with which surgeons view such an heroic measure. It implies a bold incision into the abdomen and immediate subdiaphragmatic massage of the heart until normal cardiac action is restored. It may be further necessary to incise the diaphragm in order to permit direct manipulation of the heart. Of course, intravenous fluid therapy, blood transfusions and analeptic drugs play a role in the attempt to support the circulation.

#### CASE REPORTS

*Case 1. History* (Adm. #580896). J. M., a 41 year old Puerto Rican male, was admitted to the hospital on May 19, 1948, with the diagnosis of carcinoma of the esophagus. The only symptom was progressive dysphagia of six weeks' duration. During the last week before admission, the patient was unable to swallow food or liquids of any kind. There was progressive weight loss of 32 pounds.

*Examination.* The patient showed obvious weight loss. There were a few scattered moist rales at the right base. Heart sounds were poor;  $A_2$  greater than  $P_2$ ; rhythm was regular. There was no cardiac enlargement. Blood pressure, 110 systolic and 74 diastolic. Pulse rate, 90 per minute. Vital capacity was 2.8 liters.



*Laboratory data.* Electrocardiogram revealed a vertically placed heart. Hemoglobin, 17.3 Gm. White blood count, 4050. Total protein 6.7 Gm. The Wassermann was negative, but the Kahn test was 2 plus positive. Blood chlorides, 597 mg. per cent. Urine was negative.

*Esophagoscopy.* At a distance of 31 cm. from the incisor teeth, a large, white, bleeding mass occluded the entire lumen. Biopsy showed a squamous cell carcinoma of the esophagus.

*Operation.* The patient was prepared for ten days with parenteral fluids, blood and amino acids. Penicillin aerosol was insufflated for four days. On May 28, 1948, a trans-thoracic resection of the esophagus and upper stomach with supra-aortic anastomosis was performed. The patient was premedicated with Magendie's solution,  $\mu\text{vj}$ , and atropine sulphate, gr. 1/150, at 12:15 p.m. Anesthesia sequence was nitrous oxide-oxygen-ether, using an intratracheal tube with an inflatable cuff, and employing the closed carbon dioxide absorption technique. Before induction, the patient's blood pressure was 150 systolic and 50 diastolic, and the pulse was 100 per minute. Induction of anesthesia was started at 1:16 p.m. and was quite smooth. Thirteen minutes later, the patient was intubated with a #36 anode endotracheal tube under direct laryngoscopy. The operation was started at 1:40 p.m. and proceeded uneventfully until 3:10 p.m. During this interval, the patient had been receiving blood and was in excellent condition.

At 3:10 p.m. the resident anesthetist noticed that the patient's respirations suddenly became quite shallow and then disappeared entirely. The anesthesia was discontinued immediately, but attempts to inflate the lungs by manual pressure on the rebreathing bag were to no avail. The endotracheal tube was disconnected for a moment and sucked out. Only a small amount of mucus was obtained. Another attempt to inflate the lungs was immediately made, this time by direct mouth-to-tube insufflation, but an obstruction somewhere in the tracheobronchial tree prevented ingress of air. The endotracheal tube was withdrawn slightly to obviate the possibility of its kinking against the carina, but still the obstruction persisted. At this moment it was decided that an inspissated mucus plug was probably obstructing the main bronchi. The patient during these six minutes became progressively more and more cyanotic, and the pupils were widely dilated. The exposed left lung remained collapsed. The heart began to falter and stopped beating. Death appeared imminent. The surgeon was instructed to institute cardiac massage through the open left chest which afforded easy and direct access to the heart. Again the endotracheal tube was removed, and an ordinary oro-pharyngeal airway inserted through which mouth-to-mouth insufflation of the lungs was attempted. After several unsuccessful attempts to blow air past the obstruction, the anesthetist used more than ordinary force in his mouth-to-mouth breathing. Suddenly he experienced a sensation of "something giving way" and immediately the surgeon notified him of the commencing inflation of the left lung. This mouth-to-mouth insufflation was continued for a few moments. The patient's color improved at once. A face mask was applied and artificial respiration with 100 per cent oxygen was administered by moderate pressure on the rebreathing bag. The lungs were inflated to their full capacity. Spontaneous respirations returned within a few moments. The asystolic heart assumed its normal contractions.

During the period of complete cessation of respiration and asystole, no pulse or blood pressure could be obtained. Nineteen minutes elapsed before spontaneous respirations and normal cardiac rhythm were restored. The blood pressure was recorded at 105 systolic and 78 diastolic and the pulse 120 per minute. The operation was continued to completion, which took an additional one hour and 35 minutes.

About one hour after the start of the operation, the right pleural cavity had been entered during the course of freeing the adherent tumor. Efforts to close the opening were unsuccessful, and a gauze packing was placed over the opening which sealed it effectively for the time being. At the conclusion of the operation, the stomach was sutured to the right mediastinal pleura, closing over the opening into the right pleura. The patient at the termination of the operation was in fair condition, blood pressure 80 systolic and 60 diastolic,

and the pulse rate was 112 per minute. Underwater drainage was established, and all the trapped air expelled from the chest by maintaining the lungs in their fully expanded position in the thorax. The patient had been receiving blood throughout the entire procedure, and was returned to the ward with the transfusion still going. He was placed in an oxygen tent immediately.

*Course.* On the first postoperative day, the patient was found to have a tension pneumothorax on the right side. Without moving the patient, under local anesthesia a small thoracotomy was made, and a tube placed into the right chest and connected to an underwater drainage bottle. From this time on, the patient improved progressively and on the fourth postoperative day, feedings were started. His condition continued good and he was permitted out of bed on the seventh day. On the eighth day, he was feeling well and walked about the ward. The right thoracotomy tube was still in place. He returned to bed of his own volition. Suddenly, he was seized with a severe pain over the left chest anteriorly. The surgical resident saw him at once. Heart sounds were indistinctly audible and the pulse imperceptible. His skin became blanched and cold. Respirations were very shallow. In spite of the administration of caffeine, coramine and oxygen, the patient died within a period of eight to ten minutes.

*Post mortem examination.* Cause of death was rupture of the aorta with exsanguination. Hemorrhage into left pleural cavity amounted to 2000 cc. Other findings were partial dehiscence of the esophago-gastrostomy, but no evidence of pleural infection. Purulent bronchitis of right upper and middle lobes of the lung; infarct of the upper pole of the spleen; focal fibrinous pericarditis.

*Comment.* In this case sudden interference with the respiratory exchange was apparently due to a block (? mucus plug) in one or both main bronchi. When suction and pressure methods failed, mouth-to-mouth insufflation of the lungs was successful in establishing an airway past the obstruction. Bronchoscopy might well have been effective if there had been time to institute this procedure.

*Case 2. History* (Adm. #580173). E. W., a 38 year old white female, 6 months pregnant, was admitted to the hospital on May 3, 1948 with the chief complaint of acute abdominal pain of two days' duration. Three hours before admission she suddenly went into shock. A transfusion of 500 cc. of blood was administered on admission. There was no vaginal bleeding.

*Examination.* The patient was a well developed, obese woman showing evidence of peripheral collapse. Pupils were small. A blowing systolic murmur heard over the entire precordium was loudest at the aortic area. Blood pressure was 106 systolic and 65 diastolic, pulse 100 per minute. The fundus of the uterus was felt about 4-5 cm. above the umbilicus. The abdomen was moderately tender throughout, but particularly on the right side which was rigid. Fetal heart sounds or movements could not be elicited. A large mass (fetal head?) filled the pelvis. The cervix was pulled up under the symphysis.

*Laboratory data.* Hemoglobin, 11 Gm. white blood count, 16,700; urine, 1 plus albumin with 2 plus acetone; urea nitrogen, 12 mg. per cent; Wassermann negative.

*X-ray examination.* Flat plate of the abdomen revealed a large mass extending up into the abdomen from the pelvis within which there was a row of calcific densities which had the appearance of a fetal spine and ribs.

The patient was observed for three days. Transfusions of 500 cc. of blood were given daily, but despite all conservative efforts her condition became progressively worse. A preoperative diagnosis was made of premature separation of the placenta and a degenerating fibroid of the uterus.

*Operation.* Demerol, 100 mg., and scopolamine, gr. 1/150 (hypo), were given at 1 p.m. She was anesthetized with ethylene-oxygen-ether sequence. Induction of anesthesia was started at 2:15 p.m. The patient's blood pressure was 140 systolic and 100 diastolic and the pulse rate 102 per minute. On opening the abdomen the uterus was found to be en-

larged to the size of a six months' gravidity. It had a large, soft fibroid arising from the posterior wall and filling the cul-de-sac. The right lateral wall of the uterus was soft and showed evidence of a perforation sealed over by blood clot and omentum. A supravaginal hysterectomy, incorporating a Porro Cesarean section, was performed. A live baby was delivered which required resuscitation. (The child lived for ten hours.) The hysterectomy was completed in about 35 minutes.

*Course.* The surgeon had closed the peritoncum with difficulty. The anesthetist was notified and attempted to deepen the anesthesia. At this time he noticed dark brown fluid running down the patient's cheeks and forehead from beneath the face mask. Upon removing the mask the patient's face and mouth were full of vomitus. At this time the patient ceased spontaneous breathing and the pupils became widely dilated. The patient became intensely cyanotic. The mouth and pharynx were suctioned free of vomitus, and attempts at direct transoral tracheal intubation were made. In view of the steep Trendelenberg position, this maneuver was unsuccessful and trauma to the posterior wall of the pharynx was inflicted. Another unsuccessful attempt at tracheal intubation was made by the anesthetist in charge. A provisional diagnosis of overdosage with anesthetic agent was made. No attempt was made to level out the operating table lest the patient aspirate the vomitus into her tracheo-bronchial tree. After complete suction of the mouth and nasopharynx, an ordinary metal oropharyngeal airway was inserted. At this time, the patient was deeply cyanotic and mottled. No blood pressure or pulse could be obtained.

The surgeon was immediately requested to reopen the abdomen and start subdiaphragmatic cardiac massage. Coincidentally, mouth-to-mouth insufflation of the lungs was instituted with slight but definite improvement in the patient's color. The face mask was then reapplied and artificial respiration with 100 per cent oxygen substituted. Upon opening the abdomen the heart was in complete asystole, although at one time it appeared to the surgical resident as if the heart were "quivering." However, in spite of cardiac massage the heart failed to maintain its coordinated spontaneous action, and began to falter a second time. Cardiac massage was therefore continued.

The rebreathing bag was emptied and refilled with oxygen some 12 to 15 times. The patient's color continued to improve. Cardiac massage and artificial respiration were maintained for approximately 15 minutes before spontaneous respirations and sustained heart action returned. The blood pressure and pulse rate were not recorded at this time. After reassuring the surgeon that the patient's condition was satisfactory, the abdomen was closed with through and through sutures.

Bronchoscopy was suggested and attempted but the bronchoscopist could not introduce the scope beyond the pharynx. The mouth and pharynx were again suctioned of all blood and vomitus, and the patient was returned to the ward in good condition. She was placed in an oxygen tent immediately. A transfusion of 1000 cc. of blood was started at once. Penicillin therapy was begun. The tent was discontinued on the third postoperative day. The temperature was normal; blood pressure, 110 systolic and 80 diastolic; the pulse was 100 per minute. The patient continued to do well and was discharged on the thirteenth postoperative day in good condition. In follow-up visits, she was apparently well.

*Comment.* Cause of respiratory failure in this case was most probably due to overdosage of anesthetic. Here, too, mouth-to-mouth insufflation of the lungs was effective in initiating spontaneous respiration. Cardiac massage, promptly administered and maintained, was life saving.

#### SUMMARY

Two cases are presented which illustrate an effective routine for resuscitation in the operating room.

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# PREOPERATIVE AND POSTOPERATIVE CARE OF CHILDREN<sup>1</sup>

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To anyone who has taken an interest in the surgery of early life, it must have become apparent that the child is subject to almost all the diseases of adults and to many other conditions not found in the adult. These facts were recognized some years ago when the specialty of pediatrics was developed. It is only in comparatively recent years that the same variants in the different age groups have been recognized to exist in the surgical field. From a surgical point of view, however, Barrington-Ward made an apt statement when he said "The adult may safely be treated as a child, but the converse can lead to disaster." The child is not simply a diminutive adult and cannot be so treated.

*Preoperative precautions.* Before an elective operation is performed, every effort must be made to rule out an acute or some exanthematous infection. If the child has been exposed to one of the exanthemata, hospitalization and the operation, if elective, should be postponed until after the incubation period has passed. If there is a beginning coryza, a persistent cough or reddening of the pharynx, even in the absence of fever, all but emergency operations should be deferred until the presence or absence of a definite upper respiratory disturbance can be determined. If the temperature is elevated one or more degrees before operation and cannot be accounted for by the surgical condition, the operation must be deferred until the temperature has returned to normal or the cause for the fever is found. Evidence of an active or subsiding respiratory infection, of course, always calls for postponement of the operation.

Prolonged hospitalization of children, especially in a ward to which acute cases are admitted, may be fraught with danger. Children are particularly susceptible to respiratory infections, and sooner or later, with prolonged hospitalization, they are bound to be exposed to the more common ones. It is, therefore, wise to terminate the hospital stay at the earliest moment compatible with adequate surgical aftercare.

*Fluid balance.* In considering the preoperative and postoperative care of children, the matter of fluid intake is of prime importance. For an adequate fluid intake, an infant requires about 150 cc. per Kg. body weight per day. There is a gradual drop in fluid requirements in older children: age 2 years, 125 cc.; 4 years, 110 cc.; 6 years, 100 cc.; 10 years, 85 cc.; and 14 years, 60 cc. per Kg. per day. Disturbances of fluid and electrolyte equilibrium associated with dehydration, acidosis, and alkalosis necessitate an increase in these amounts of fluid. In infants, acidosis may result from excessive losses of cations (Na and K) and bicarbonate in diarrhea. Alkalosis is most often associated with severe and persistent vomiting, when the hydrochloric acid of the gastric juice is lost in the vomitus—this state is commonly noted in infants with congenital hypertrophic pyloric stenosis. In severe dehydration, whether with acidosis or alkalosis, oliguria develops. (In nonactive infants urinary output is 200 to 500 cc. per day;

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in children, 500 to 800 cc.) Thirst may be present, but is by no means constant. The physical signs are loss of weight; grayish pallor, dryness, inelasticity and diminished turgor of the skin; dryness of the mucous membranes; sunken fontanels in infants; retracted abdomen and collapsed superficial veins. Fever may be present, ascribable to dehydration as well as to an attendant infection. In the diagnosis of acidosis or alkalosis, blood determinations should be made on the basis that the normal carbon dioxide content of the blood is 50 to 60 volumes per cent. In dehydration, evidence of hemoconcentration may be found in an elevated volume of red blood cells (above 50 per cent hematocrit reading), in an increased red blood cell count (above 5 million), and in an increased concentration of serum protein (above 6.5 Gm. per 100 cc.). The patient who is dehydrated before operation requires 6 per cent of his body weight in replacement fluid (60 cc. per Kg.) if the dehydration is to be overcome. The loss of fluids associated with operation further depletes the body fluids.

In severely ill children intravenous fluids are administered continuously. A mixture of 10 per cent dextrose in distilled water and 5 per cent dextrose in isotonic solution of sodium chloride is advised. In infants and young children it is preferable to expose a vein at the ankle and to tie a cannula in place; for this purpose a Karelitz needle (No. 542 L.N.R.; Becton, Dickinson and Co.) is very useful.

In the treatment of shock, the type and amount of fluids required for the restoration of a depleted blood volume will depend on the nature of the conditions leading to the shock state. Thus, hemorrhage or skeletal injuries with hemodilution require transfusions of whole blood, whereas after burns or crushing injuries of soft tissues with hemoconcentration plasma is needed rather than whole blood. The amount of blood or plasma given is usually about 15 cc. per Kg. body weight. Determinations of hemoglobin content, hematocrit, red blood cell count, and plasma protein afford indices of hemodilution or hemoconcentration.

The parenteral administration of solutions of amino acids has many advantages, since in this way water, minerals, dextrose, and nitrogen may be supplied simultaneously. Amino acids are indicated when the alimentary tract is obstructed; when the gastrointestinal tract should be kept at rest as during the postoperative course of abdominal surgery; when a patient, because of any acute or chronic disease, is unable to take sufficient food by mouth; when protein cannot be properly assimilated, as in protracted diarrhea. Preparations of protein hydrolysates (**Amigen** or **Paranamine**) can be administered intravenously or subcutaneously when diluted with 5 per cent dextrose. The amount to be administered will depend upon the condition and the size of the child. At least 1 Gm. of amino acids per Kg. of body weight per day should be used. Reactions to the parenteral administration of amino acids are usually caused by too rapid rate of injection. The solution should be given slowly at the rate of about 1 cc. per minute to an infant, and not faster than 5 cc. per minute to an older child. When there is a significant deficit of serum protein, blood plasma can be provided in addition to the amino acids. Recent reports of hepatitis

following the administration of pooled plasma have drawn attention to the dangers of blood plasma, and transfusions of whole blood are preferable.

*The nutritional requirements* of children will be briefly outlined, since the topic can be more adequately treated by the pediatrician. The approximate daily caloric requirements of children are as follows: beginning with an average of 110 calories per Kg. of body weight per day during the first year of life, there is an approximate decrease of 10 calories per Kg. in the daily requirements for each 3 year period. The protein requirements start with 4 Gm. per Kg. of body weight per day during the first year of life, and an approximate decrease of 0.5 Gm. per Kg. in the daily requirements for each 3 year period. The remainder of the daily requirements to meet caloric needs is supplied by about 35 per cent of fat and 50 per cent of carbohydrates.

It is now well established that vitamins are organic substances which occur in many foods and are essential for the normal functioning of the body. Those which have been proven to be most needed are vitamins D, C, A, K, niacin, riboflavin, and thiamine. In considering their basic requirements in the post-operative care of infants and children, it is generally recognized that the diets of infants and children are more likely to be deficient in sterols containing vitamin D activity than in any of the other food essentials. Since vitamin D is inadequately supplied in the neutral diet, all children should receive supplements of cod liver oil or substances having vitamin D activity sufficient to supply from 400 to 800 I.U. daily. Fish liver oils (percomorph, cod, halibut) constitute the chief dietary sources of vitamin D. A number of preparations containing activated ergosterol are available in water soluble form (2 drops of percomorph oil, drisdol or viosterol and 1 teaspoon of cod liver oil contain about 400 I.U.). Because cow's milk, which makes up such a great part of their diet, is notoriously poor in vitamin C (ascorbic acid), young children and especially infants require supplements of ascorbic acid. The chief sources of ascorbic acid are citrus fruit and tomatoes. Orange juice contains about 0.5 mg. per cc. The approximate daily requirements of vitamin C in children are 30 mg. under 1 year of life up to 90 mg. at 15 years. Vitamin A is supplied in liberal quantities in the diet of children, so that deficiency symptoms from its lack seldom develop, and the fish liver oils discussed in connection with vitamin D will take care of their requirements. The daily requirement of the vitamin B complex (niacin, riboflavin and thiamine) are usually met by an adequate protein intake. Vitamin K is of special interest because it is concerned with prothrombin production and because of its role in hemorrhagic disease of the newborn. It is good practice to administer 1 to 2 mg. of menadione subcutaneously after birth. It is not required later except in children with obstruction of the bile ducts or liver disease.

The uses of sulfonamides and antibiotics in the treatment of infections are well known. The intravenous administration of the sulfonamides is advisable in seriously ill patients to establish effective blood levels as soon as possible. For this purpose, a 2 per cent solution of sodium sulfadiazine in sterile distilled water is recommended. The initial dose of the solution is 2.5 cc. per pound of body weight, followed by a maintenance dose of 5 cc. per pound per day divided into

3 doses. To prevent urolithiasis, sodium lactate is administered intravenously as  $\frac{1}{6}$  molar solution following the sodium sulfadiazine; the amount is twice the number of cc. of the sodium sulfadiazine. When intravenous fluids are stopped the sulfadiazine can be given orally in total daily doses of 1 grain per pound of body weight (0.1 Gm. per Kg.). This is divided into 6 equal portions and administered at 4 hour intervals with additional sodium bicarbonate. The drug should be continued for 48 hours after a good response, and the dose then halved and given for 2 or 3 days. For example, 1 year old infants require a daily total (divided into 6 doses) of 1 Gm., 2 year old children 2 Gm., and 3 year old and older children 3 Gm., in addition to an initial dose of these same amounts. A recent development in sulfonamide therapy has been the combination of sulfanilamide, sulfathiazole and sulfadiazine which is reported to eliminate the complication of urolithiasis and does not necessitate the use of alkalis. There are no clearly defined dosages of penicillin for infants and young children, and dosage in the individual case can only be determined by the clinical response. For children with severe infections, a total daily dose of 80,000 units in an infant and 160,000 units for a child are minimal. Penicillin is gradually replacing sulfa therapy because of the low incidence of toxic effects and its efficacy in surgical infections with the pneumococcus, streptococcus, gonococcus, *C. tetani*, and *C. Welchii*, but the combination of sulfonamides and penicillin is more effective. Infections with organisms susceptible to streptomycin are less frequent than infections susceptible to penicillin. Streptomycin is of especial value in checking infections of the urinary tract, provided that the organisms are susceptible ones (*E. coli*, *B. proteus*). In children, dosages of 20,000 units per pound of body weight (1 million units per Gm.) are given every 4 hours. It is important to remember that some organisms develop a resistance to the antibiotics, and it is safer to use these drugs in adequate dosage. A long experience with appendiceal peritonitis in children has demonstrated the efficacy of large doses of penicillin (as much as 800,000 units per 24 hours), notwithstanding the resistance of *E. coli* to the drug. In consideration of the use of all of these agents in the treatment of infections, the important role of adequate surgery when indicated must not be overlooked. These therapeutic aids are highly important but they have not replaced good surgery.

*Anesthesia.* The most commonly used anesthetic agents in infants are vinethane and ether; in older children, ethylene and cyclopropane. The preparation of children for anesthesia must be carefully carried out; a child brought to the operating room with inadequate preoperative sedation and physically restrained while going under anesthesia suffers a severe psychic trauma necessitating an excess of the anesthetic agent and this may result in respiratory complications. The following procedures are advised: for infants, atropine; for children from 2 to 12 years old, sodium pentothal or nembutal by rectum, and atropine; for children over 12 years of age, morphine and scopolamine. These drugs should be given at least one-half hour before operation. The dosage is outlined in table 1.

Sodium pentothal and nembutal, when used by rectum, are simply adminis-



tered and, in the proper dosage, non-toxic. No other sedatives are administered when they are used. A preliminary enema is not required if there has been a bowel movement on the day of operation; if an enema is necessary in preparation for operation, use tap water or normal saline several hours before operation. The dosage rule of sodium pentothal is 1 Gm. for every 50 pounds of body weight. A 3 Gm. vial of sodium pentothal is dissolved in 30 cc. of distilled water (1 Gm. per 10 cc., or 0.1 Gm. per cc.). The drug is instilled into the rectum by a syringe through a catheter about half an hour before moving the patient to the operating room. The only contraindications to this procedure are respiratory impairment and operations on the nose or throat.

*Postoperative care.* The analgesics used after operation are codeine and aspirin; these are effectively combined in a rectal suppository. The doses of codeine are as follows: 1 month,  $\frac{1}{30}$  grain; 3 months,  $\frac{1}{25}$  grain; 1 year,  $\frac{1}{8}$  grain; 2 years,  $\frac{1}{6}$  grain; 5 years,  $\frac{1}{4}$  grain. The usual dosage of aspirin is 1 grain per year up to the age of 5 years; doses larger than 5 grains are seldom necessary.

TABLE 1

AGE	ATROPINE	NEMBUTAL	MORPHINE	SCOPOLAMINE
	<i>grain</i>	<i>grain</i>	<i>grain</i>	<i>grain</i>
Up to 2 mos.	1/1000			
2-12 mos.	1/750			
1-2 yrs.	1/500			
2-4 yrs.	1/350	1½		
4-6 yrs.	1/300	3		
6-8 yrs.	1/250	3		
8-12 yrs.	1/200	5		
12-14 yrs.	1/150		1/12	1/150

Dressings are applied in such a manner that the wound is not easily contaminated by urine or feces. For example, following hernioplasty in an infant a small collodion dressing is applied, the arms and legs are restrained by padded cuffs, a cradle keeps the bed clothing off the body, and a diaper is suspended from the lower end of the cradle and catches urine.

In the treatment of postoperative pulmonary complications the use of sulfonamides and antibiotics has been discussed. Severe dyspnea, with or without cyanosis, is an indication for oxygen therapy. The early administration of oxygen will greatly reduce the needs for sedatives and analgesics and will do much to quiet the restless, pneumonic child. Oxygen is best supplied through a tent or cubicle. The temperature of the air within the tent is maintained at a considerably higher level than is customary with oxygen tents in adults, and ice is not used in the infants' tents. When there is an excessive accumulation of secretions in the larger air passages during operation, bronchoscopic removal is indicated. Aspiration of infected material during or following any operation under general anesthesia is a frequent mechanism for the production of pulmonary atelectasis or abscess. Treatment of pulmonary complications should be

guided by repeated x-rays of the chest. The problem of pulmonary embolization is of no great concern in childhood. The fact that children move their lower extremities so actively after operation may be a factor in this low incidence.

Vomiting and abdominal distention are controlled by the passage of a catheter or Levin tube into the stomach and maintenance of gastric siphonage as long as intestinal or biliary drainage continues. Prostigmine is useful in the occasional occurrence of reflex abdominal distention; subcutaneous doses of 0.5 to 1 cc. of a 1:4000 solution may be employed. The use of the plain roentgen film of the abdomen is the most important diagnostic aid in the diagnosis and management of intestinal obstruction.

In the consideration of postoperative shock in infants, prevention plays an important rôle. The surgeon should be accustomed to the handling of the delicate tissues of the infant and to the gentle use of small instruments and suture material; this is more important than speed. Rough handling of tissue, blood loss and exposure to cold are very shocking to infants. The principles of fluid requirements and method of administration have been discussed. External heat by hot water bottles or warm blankets is useful during operation. Inhalations of oxygen supplied by means of a tent or cubicle are used after prolonged operations. If the infant is premature, or if difficulty should be experienced in maintaining body temperature at a normal level, the patient is placed in an incubator.

#### SUMMARY

The principles of preoperative and postoperative care of children are presented. The fluid intake and the nutritional requirements of children, the problems of anesthesia, and the treatment of postoperative shock and infections are outlined.

# THE PRESENT STATUS OF THE SURGICAL TREATMENT FOR COARCTATION OF THE AORTA<sup>1</sup>

ELLIOTT S. HURWITT, M.D.<sup>2</sup>

Coarctation of the aorta is a congenital anomaly characterized anatomically by a narrowed segment in the descending portion of the aortic arch, frequently at or just below the attachment of the ligamentum arteriosum. The diagnosis may usually be suspected clinically on the basis of hypertension in the arms associated with diminished or absent pulsations in the legs. Frequently there is a systolic murmur over the precordium, heard also over the interscapular area; the pulsation of collateral vessels in the thoracic wall may also be palpated. Simultaneous arm and leg pulse tracings show a delay in the transmission of the pulse, and plethysmographic recordings reveal a decrease in the blood volume flow in the lower extremities. Roentgen examination of the chest may show scalloping of the inferior rib borders; rarely the actual area of decreased calibre of the aorta is visible in an oblique view. Angiocardiography has provided definitive delineation of the lesion (12).

Until very recently the prognosis has been poor for patients exhibiting this defect. Maude Abbott, in 1928, published a study of the autopsy protocols of 200 cases of coarctation in subjects above the age of 2 years (1). She found that 74 per cent of these patients died before their forty-first year. In 1947, Reifenshtein, Levine, and Gross analyzed 104 autopsied cases collected from the literature since the previous review, revealing a mortality of 61 per cent by the age of 41 (22). Approximately 75 per cent of these deaths were attributable to complications of the coarctation, including rupture of the aorta, subacute bacterial endocarditis or endarteritis, cardiac decompensation, or cerebral hemorrhage. Blackford pointed out that in a group of 180 patients living beyond the age of 5 years, only 68 survived to the forty-first year (2).

The surgical treatment of coarctation of the aorta is a logical development both of extensive animal experimentation and of careful clinical observation. Figure 1 is a composite diagram showing the present status of the various procedures in current usage. Gross and Hufnagel, in September 1945, published their description of resection of the area of narrowing, followed by anastomosis of the 2 segments of aorta (Figs. 1-3). The protocols of their animal experiments date back to 1938; Gross first performed the operation on a child on June 28, 1945 (13). Crafoord, encouraged by the feasibility of clamping the thoracic aorta in the course of a thoracotomy for patent ductus arteriosus, had carried out an essentially similar procedure on October 19, 1944; his report appeared in October 1945 (11). Subsequent papers indicate that this is the procedure of choice, when the local anatomical features permit (14, 15). At the present time Gross has performed removal of the coarctation from 36 patients, with 5 deaths (16).

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Anastomosis of the left subclavian artery to the aorta below the coarctation (Figs. 4-6) may be preferable under certain circumstances. Blalock and Park,

Surgical procedures employed in correction of coarctation of aorta

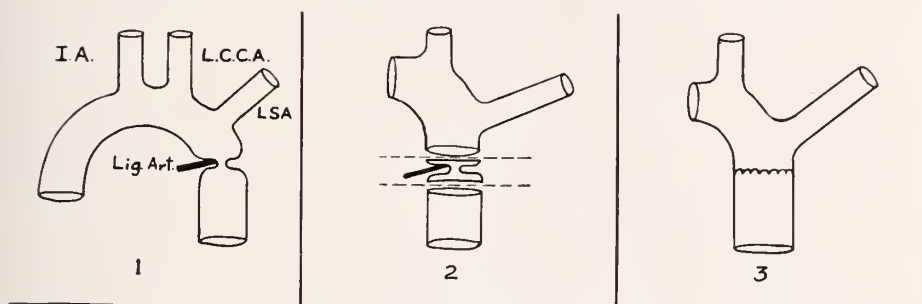


FIG. 1. Resection of coarctation

FIG. 2. End to end anastomosis of aorta—Crafoord

FIG. 3. Gross

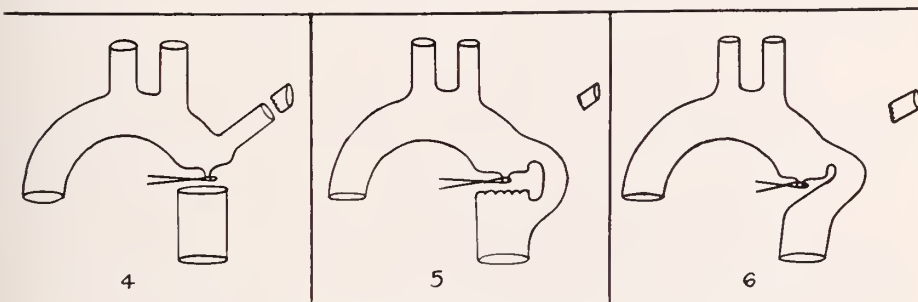


FIG. 4. Anastomosis of left subclavian artery to aorta

FIG. 5. End to side—Blalock

FIG. 6. End to end—Clagett

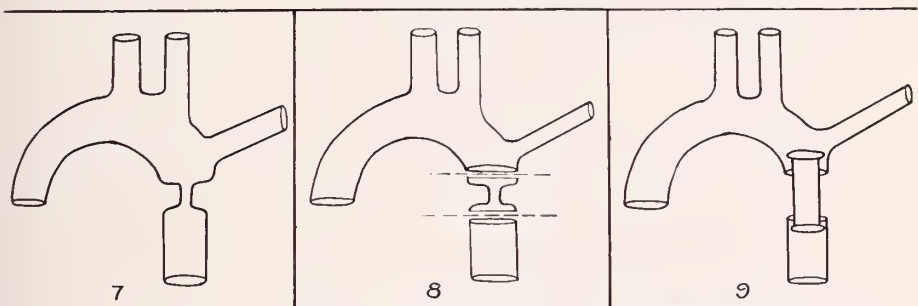


FIG. 7. Replacement of narrowed segment (experimental) lucite tube—Hufnagel

FIG. 8. Polyethylene tube—Hackworth

FIG. 9. Aortic homograft—Gross and Hurwitt

in 1944, described anastomosis of the proximal end of the divided left subclavian artery to the side of the aorta, in a series of experiments on dogs (4). Blalock subsequently completed this procedure in human subjects, although in most of



his cases the operation of Gross was utilized (5). Clagett performed 16 operations for coarctation; about two-thirds had end-to-end anastomosis of the aorta and in one-third the subclavian was used (8). In the latter group the end-to-side procedure of Blalock was employed once, and in 4 cases the end of the subclavian artery was anastomosed to the end of the lower segment of aorta (Fig. 6). The subclavian artery has also been used successfully by Bradshaw (6). This procedure is most useful when the narrowed segment is situated so closely to the origin of the subclavian artery that direct suture anastomosis of the aorta would not be possible, as in Clagett's case (9). It may also be preferable when the coarctation is so long that considerable tension would be required to approximate the divided ends of the aorta.

There remains a small group of cases not amenable to correction by either of the techniques described above. Rarely the segment of coarctation may be too long to permit either end-to-end anastomosis of the aorta or the subclavian bypassing procedure. Cases have also been encountered in which only 2 large arterial trunks arose from the arch of the aorta, eliminating the subclavian from consideration.

It is for such cases that an alternate method of bridging the gap must be found. This has been accomplished by various means in animals (Figs. 7-9). The divided ends of the dog aorta have been successfully joined by a segment of human popliteal artery (Carrel, 7); by vitallium tubes lined with human saphenous vein (Blakemore and Lord, 3) and with turkey jugular vein (Copley and Stefko, 10); by lucite (Hufnagel, 19) and polyethylene (Hackworth, 18) prostheses; and by both fresh and preserved segments of aorta obtained from other dogs (Gross and Hurwitt, 17; Hufnagel, 20). The application of these results to the field of human surgery is hardly justified at the present stage of their development. Little has been added to the histologic knowledge of the fate of homotransplants and heterotransplants of blood vessels since the publication of Neuhof's monograph in 1923 (21). Studies now in progress, with the aid of antibiotics and modern techniques, may be expected to shed additional light on this subject.

The optimum age for operation also remains to be determined. The importance of eliminating the hypertension before irreversible cerebral, renal, or vasomotor changes may have occurred is obvious. Operation in the older age group is further complicated by atherosclerotic changes in the wall of the aorta, resulting in a decreased tissue elasticity and jeopardizing the success of the suture line. On the other hand, the small size of the structures involved would cause one to hesitate to attempt the procedure in the very young. Another objection to operating too early is the incompleteness of the data at the present time of the fate of such an anastomosis in terms of growth of the remainder of the aorta. If the anastomotic site were to remain of fixed size while the aorta above and below increased in diameter, a relative coarctation would again occur. Work is being carried out in this laboratory to clarify this point. At present the ages of the reported operated cases range from 5 years (Gross, 14) to 34

years (Clagett, 9). Gross has preferred to wait in the younger patients until about the age of 8 years (15). In some subjects too old for direct surgery upon the aorta, improvement may be anticipated by eliminating the vasospastic component of the hypertension, as suggested in the article by Reifenstein, Levine, and Gross (22).

It is felt that the surgical procedures currently employed in the treatment of coarctation of the aorta offer a greatly improved prognosis for patients with this lesion. The post-operative mortality of 5 deaths in 36 resections, obtained by Gross (16), compares very favorably at the present time with the high mortality in the unoperated series. Postoperative improvement has been marked, with a decline in the hypertension, and the appearance of pulsations in the lower extremities; in only 1 of the cases in Dr. Gross' series was there failure to relieve the hypertension. It is too soon to evaluate this improvement in terms of longevity. Because of the incidence of associated congenital anomalies in a number of cases, such as a bicuspid aortic valve or intracranial aneurysms, further complications may be anticipated. This, however, should in no way be allowed to detract from the very real progress that has been made in this field.

#### SUMMARY

The present status of the surgical treatment of coarctation of the aorta has been presented.

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## A METHOD OF OBTAINING INTRACARDIAL ELECTROGRAMS DURING CARDIAC CATHETERIZATION\*

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M.D., SIGMUND BRAHMS, M.D. AND MARCY L. SUSSMAN, M.D.

Heart catheterization is an important investigative tool in modern clinical cardiology, particularly in the integrated study of congenital heart disease. The results of chemical studies of blood from the right chambers and pulmonary artery, as well as endocardial pressure recordings, are often of paramount importance in the decision as to whether a patient should be subjected to surgical intervention or rejected as unsuitable for this therapy. It is somewhat different with endocardial electrocardiography. While interesting and important from the viewpoint of research, it has not been demonstrated that endocardial electrocardiography is required in the interest of the patient. This consideration led to the thought that it would be desirable, if possible, to combine cardiac catheterization with intracardial electrography in those cases where the former is required.

In our first trials, the metallic hub of the Cournand catheter was connected with the chest lead wire of the electrocardiograph, using the blood or saline contents of the catheter as a conducting medium. This arrangement provided satisfactory results, as shown in Figure 1. However, due to the high resistance of the long fluid column, interference by induced alternating current could not always be eliminated (fig. 1).

We therefore finally used the following method, which was suggested by Dr. Sergei Feitelberg. A thin wire is introduced into the catheter, one end being soldered to the metallic hub of the catheter and the other end extending to within a few millimeters of its flexible tip. We use a copper-nickel alloy wire with a resistance of 5.86 ohms per foot. The wire is of gauge 33 (B&S), thickness 0.007 inches, which does not seriously diminish the flexibility or narrow the lumen of the catheter and does not interfere with the aspiration of blood specimens. There is possibly a slightly greater tendency for clotting to occur in the catheter, especially when the tip is in a high pressure area. However, this is minimized by increasing the pressure in the continuous intravenous saline infusion system when the catheter enters these areas.

As can be seen from Figure 2, the tracings registered with this improved method show practically no interference by alternating current, even when a high film speed is used.

In this method of endocardial electrocardiography, in contrast to the conventional endocardial recording, artefacts due to contact or pressure of the metallic sound (which are represented chiefly by a high upward displacement of the ST segment and distortion of the S wave or even the RS complex) are rarely encountered. Another advantage of our type of conductive heart catheter is the

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fact that electrograms made by this method represent the changes in the electric potential within all or part of the contents of the cardiac cavity under investigation. While the electrode may occasionally be located in the middle of the heart cavity in the metallic sound method, in all likelihood it usually touches

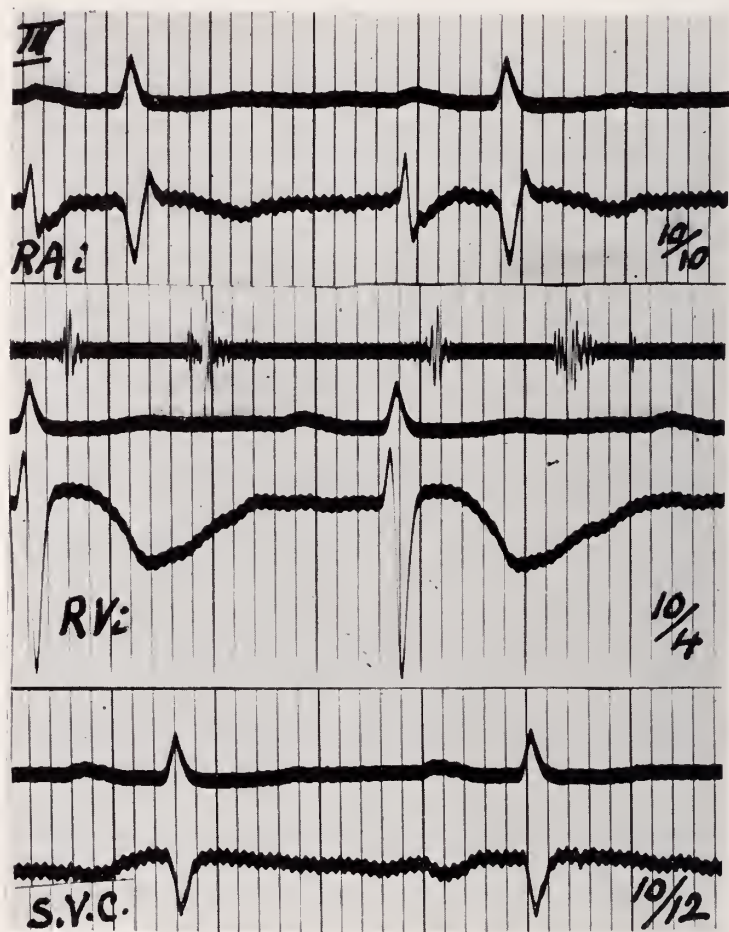


FIG. 1. Intracardial electrograms made consecutively in the same patient from within right auricle (RA), right ventricle (RV) and superior vena cava (S.V.C.). The upper electrocardiograms in each tracing are standard lead III. Standardization in millimeters/millivolts is given in the right lower corner of each tracing. The intracardiac tracings were made from the hub of the catheter: no indwelling wire was used.

the endocardium. The tracings, in this case, presumably represent a mixture of the electrical behavior of the contents of the cavity and that part of the endocardium touched by the catheter, including artefacts due to the latter cause.

*Summary.* A method is described of making intracardial electrograms from those cardiac chambers and great vessels which are reached during cardiac

catheterization. The usual Courmand intracardiac catheter is used as an electrode, with or without an indwelling wire. The wire eliminates alternating

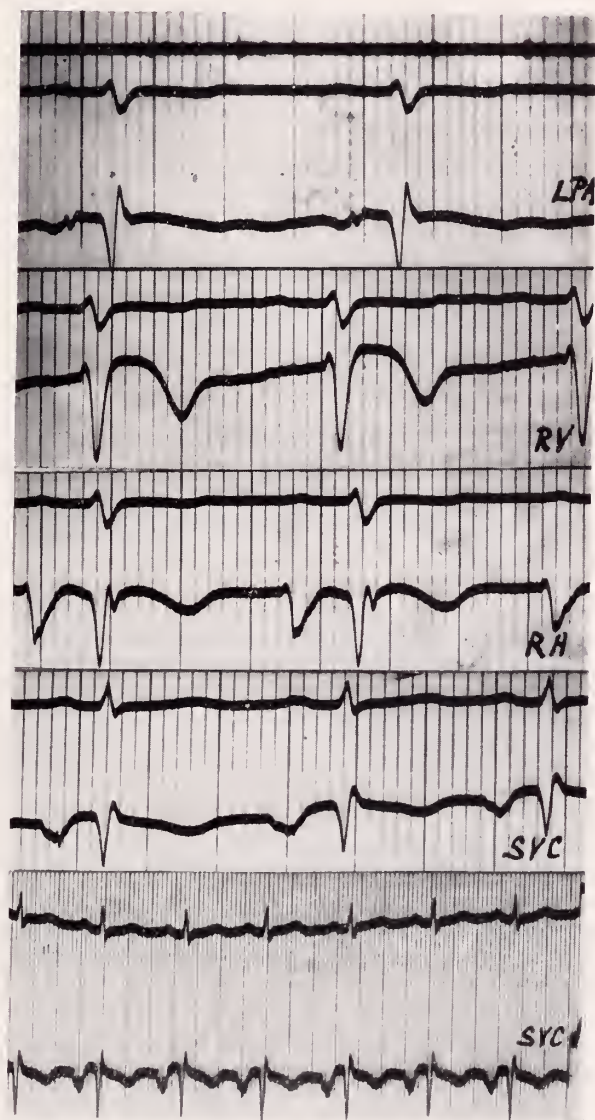


FIG. 2. Intracardiac electrograms made consecutively in the same patient from within the left pulmonary artery (LPA), right ventricle (RV), right auricle (RA), and superior vena cava (SVC). The latter tracing was also made with low speed. The intracardiac tracings were made from the hub of the catheter, to which was soldered an indwelling wire.

current interference and does not interfere with the usual pressure recordings or with the obtaining of blood samples for chemical analysis.

## HYPERNEPHROMA IN A HORSESHOE KIDNEY<sup>1</sup>

GORDON D. OPPENHEIMER, M.D.

Anomalies of the genito-urinary tract and particularly of the upper urinary tract are of common occurrence and clinically important. One of the most interesting anomalies is that of horseshoe kidney which has been known as an anatomical curiosity since the earliest days of cadaver dissection. As far back as 1522 Da Carpi described such a case and Morgagni (1) gave a good anatomical description of the lesion. Rayner (2) in 1837 illustrated the condition in his atlas stressing the usual fixation of the renal mass and its compression on the abdominal vessels. Since the advent of retrograde and excretory urography, horseshoe kidneys have been a more frequent clinical finding. Lipshutz and Hoffman (3) in a collected statistical study of 70,502 postmortem examinations found 105 horseshoe kidneys with an estimated ratio of one case in every 671 examined. Gutierrez (4) estimates the frequency at about one in 200 pyelograms.

While the lesion is obviously a congenital malformation, the etiology is unknown. Fusion of kidneys when it occurs must take place at an early period of intrauterine life. Thus Felix observed a fused kidney in a 30 mm. embryo (about 55 days); Schaeffer found the two renal blastemata fused in a 100 day embryo.

The ordinary symmetrical horseshoe kidney has the form of a typical horseshoe with the lower poles fused and with the renal pelves in front, anterior to the blood vessels. The ureters descend over the ventral surface of the isthmus of the fused organ which usually lies low in the abdomen at about the level of the aortic bifurcation. The concavity of the organ faces upward. In the true horseshoe kidney the fusing substance, or the isthmus, is made up of a solid bridge of renal parenchyma, whereas in the false type, the right and left organs are bound together solely by a fibrous tissue band. In rare instances fusion takes place in the upper poles with the concavity facing downwards. There are often asymmetrical types of fusion where one side is smaller than the other and differently positioned. Other anomalies such as reduplication of the ureters and pelves occur in horseshoe kidneys adding to the potentiality of disease which is common in this lesion. In fact Gutierrez (4) speaks about horseshoe kidney disease rather than the anatomical lesion, and with much justification. The horseshoe kidney is usually fixed to the surrounding structures and blood vessels by the isthmus. The blood vessels which supply the organ vary in size, number and position but are usually directly connected with the aorta and vena cava. Hilar vessels to both sides and vessels to the isthmus vary from case to case. The position of the kidney over the sympathetic and parasympathetic nerves and ganglia is important in the causation of the symptoms in horseshoe kidney syndrome. There are: 1. pain in the mid-abdomen with lumbar radiation, 2. gastro-intestinal complaints with chronic constipation, and 3. urinary symp-

<sup>1</sup> From the Urological Service of The Mount Sinai Hospital, New York.

toms which follow infection due to stasis. Complicating pathological features which are found in horseshoe kidneys are calculi, hydronephrosis, pyonephrosis, tuberculosis, neoplasm, polycystic disease, etc.

The diagnosis of horseshoe kidney is usually made by x-ray studies. However, in thin individuals a tumor mass extending across the abdomen can occasionally be palpated. The characteristic x-ray findings (retrograde and excretory urography) are 1. position and shape of the kidneys, 2. anterior rotation of the pelves, 3. the inward turning (reverse position) of usually the lowermost calyces and 4. high insertion of the ureters in the pelves. Gutierrez has described a "pathognomonic pyelographic horseshoe triangle." A base line is drawn horizontally between the calyces on either side nearest to the mid-line. From these calyces a line is drawn to the mid-spine at the level of the iliac crests. This lowermost angle in normal kidneys averages 90 degrees, while in horseshoe kidneys it approximates 20 degrees. Thus the diagnosis of horseshoe kidneys should not be difficult with the usual urological data at hand.

Carcinoma in a horseshoe kidney is a rare lesion. Only one of Gutierrez's 25 cases showed carcinoma. Botez (5) collected 320 cases of horseshoe kidney from the literature and found a carcinoma in one case and sarcomatous tumors involving one-half of a horseshoe kidney in four children. Rathbun (6) found four instances of neoplasm in 108 clinical cases culled from the literature.

The following case presentation illustrates the surgical therapy of this unusual condition.

*History.* (Adm. #548701) O. B., a 59 year old white male, was admitted to the Mount Sinai Hospital on May 9, 1946 complaining of painless hematuria of 3 weeks' duration. One year previously he had suffered a fractured skull which had left marked residua including a left hemiparesis and a Parkinson-like syndrome. The rest of the history was not significant. Urological study before admission had revealed left renal hematuria and excretory and retrograde urography had indicated a horseshoe kidney. The diagnosis of a carcinoma of the left half of a horseshoe kidney had been made.

*Examination* disclosed a well nourished and developed man with a mask-like facies and left hemiparesis. The heart and lungs were normal; the blood pressure was 140 systolic and 85 diastolic. In the left upper quadrant of the abdomen there was a firm, ballotable, non-tender mass with a rounded projection at its lower limit. The blood count and blood chemistry examinations were normal. The urine contained red blood cells and the cultures were negative.

An excretory urogram showed a horseshoe shaped mass which was mobile (an unusual feature) with the isthmus overlying the midlumbar spine. The upper part of the left kidney was under the twelfth rib. Function was good on both sides. The left pelvis was dilated and its calyces pointed mesially (as did the lower calyces of the right kidney). There was no evidence of compression of the calyces from the above mentioned palpable rounded area. Cystoscopy was non-contributory. Retrograde pyelography reproduced the same picture as the excretory urogram (fig. 1). The diagnosis of carcinoma involving the left half of a horseshoe kidney was confirmed.

*Course.* On May 17, 1946, through a left lumbar extra-peritoneal incision a horseshoe kidney was found containing a neoplasm in the lower portion of its left side. In addition, numerous aggregations of small simple cysts were seen. The tumor protruded anteriorly, was reddish brown in color, about 5 cm in diameter and 3 cm above the surface of the kidney. The isthmus was approximately 3 x 4 x 2 cm. in size. Mesial to the tumor and towards



the right side of the isthmus, an incision was made between rubber covered clamps into apparently normal kidney tissue, but just below the surface, tumor was seen. Therefore resection was performed at the junction of the lower third and the upper two-thirds of the right side of the fused kidney. The incision was wedge-shaped and closure was effected using Beer sutures with underpinned fat and fibrin foam tied over the cut edge. The main blood supply of the left kidney came from above near the upper pole at which point the



FIG. 1. Bilateral retrograde pyelogram. Horseshoe mass over spine. Note calyces of both kidneys which point mesially.

vessels were doubly tied and sectioned. The ureter was ligated and severed about 6 cm. below the lower border of the kidney. The wound was drained and closed in typical fashion. The patient's post-operative course and convalescence was without complication except for a minor wound infection and he was discharged from the hospital on the 26th post-operative day. The pathological report was "malignant Grawitz tumor of the left portion of horseshoe kidney showing invasion of a large renal vein. Tumor tissue is present at the line of resection."

The patient remained well for one year. He was recently admitted to another hospital with complaints of hematuria and weakness. Studies indicate a neoplasm in the remaining portion of the kidney.

#### SUMMARY

A case of a malignant Grawitz tumor involving the left half of a horseshoe kidney is presented. Extirpation of the left kidney, isthmus and lowermost portion of the right kidney was performed. Evidence of recurrence was present fifteen months later.

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## DUODENAL-COLIC FISTULA AS A COMPLICATION OF REGIONAL ILEITIS\*

HAROLD MASTERS, M.D.

The formation of fistulous tracts in the presence of regional enteritis is a common complication of the disease. Numerous anatomical distributions of the tracts have been described. However, a fistula on the basis of this disease joining duodenum and colon apparently has not been previously noted.

A case with such an occurrence is presented to emphasize the rarity of this complication and its attendant signs and symptoms.

### CASE REPORT

*History.* I. K., a man, aged 40 years, entered The Mount Sinai Hospital on December 6, 1947 with complaints of general weakness, diarrhea and abdominal pain.

In 1933 he developed lower abdominal pain and a diagnosis of acute appendicitis was made. He was operated upon and the appendix was found to be normal, but there was a terminal ileitis. The appendix was removed and the abdomen closed without further exploration.

During the next ten years, the patient had recurrent attacks of lower abdominal pain and diarrhea. He was placed on special diets without beneficial effect.

In 1943, x-ray studies revealed typical findings of a chronic terminal ileitis. He was given several courses of sulfonamide therapy without alleviation of symptoms.

In September of 1946, he was operated upon at the Mayo Clinic. The operation consisted of a resection of the terminal four feet of ileum and the ascending colon. An end to end ileocolostomy was performed.

After the operation, he was comfortable for about five months. His symptoms then reappeared. An x-ray examination at that time revealed an area of regional ileitis immediately proximal to the ileo-colic anastomosis. He had several episodes of sub-acute intestinal obstruction in November of 1947 which were treated conservatively.

On his admission to Mount Sinai Hospital, his main complaints were those of weakness, diarrhea and anorexia. He stated that since the onset of his illness he had lost 84 pounds.

*Examination.* The patient was undernourished and apprehensive. There was marked tenderness over the lower abdomen. No other positive findings were present. The laboratory tests revealed no significant abnormalities.

*Course.* A diagnosis of recurrent regional ileitis was made and operation was advised. It was carried out on December 11, 1947 by Dr. Garlock. When the abdomen was opened, distended loops of small bowel came into view. Exploration revealed that a knuckle of small bowel had become adherent to a segment of diseased ileum, causing a partial intestinal obstruction. The ileum was then examined. The distal two feet of ileum was found to be involved by an inflammatory process. The walls were friable and indurated. The lumen of the diseased bowel and the ileo-colic stoma were markedly stenosed. The remainder of the small bowel was normal. The question of what procedure should be carried out was difficult because it was obvious that without corrective measures, obstruction and accentuation of symptoms would inevitably occur. However, the presence of the obstructed bowel with its edematous, friable walls hardly made this an ideal case for any radical procedure.

An exclusion operation was decided upon. The diseased ileum was excluded, and a side to side ileo-transverse colostomy was performed well beyond the original anastomosis.

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\* From the Surgical Service of Dr. John H. Garlock.

Immediately proximal to the anastomosis, the transverse colon was transected, and the proximal limb was brought out on the abdomen as a colostomy stoma. In spite of all the small bowel distension, the procedure was carried out without incident.

On the fifth post-operative day, there was noted an excessive amount of biliary drainage from the colostomy. A fistula was of course suspected. It was reasoned that a loop of upper jejunum had become fixed to the colostomy limb, and that a spontaneous perforation had occurred, in spite of the fact that this was unique in the experience of all those conversant with the various complications of the disease. The presence of a fistula was confirmed when carmine red dye given by mouth appeared on the abdominal dressings two hours after ingestion.

The patient received supportive measures including multiple transfusions until January 21, 1948. Because the fistula showed no signs of spontaneous closure, surgery was again deemed advisable.

*Second operation.* Numerous adhesions were encountered binding various loops of bowel together. These were separated. No fistula was found in the region of the exteriorized colostomy limb. The inflammatory process in the excluded ileum had subsided considerably as compared to its previous appearance at the first operation. It was dissected free from the surrounding structures.

In view of the clinical features, the presence of a fistula had been considered a certainty. Yet no fistula could be found between normal small bowel and excluded colon. In spite of this, it was decided to proceed with the resection of the excluded ileum and transverse colon.

The site of the ileo-transverse colostomy was found to be involved by the same inflammatory process that had affected the ileum. In the mobilization of this part of the colon, it was found that there was an intimate connection between it and the duodenum. And this connection consisted of a dime-sized opening between the second portion of the duodenum and colon immediately distal to the old anastomosis. The colon was dissected away from the duodenum, and the duodenal opening was closed in two layers. The diseased ileum and colon were then resected. The adherent loops of ileum and jejunum were then separated from each other down to the ligament of Treitz. It has been the experience of this Service that in this disease these separated loops rarely adhere again in such a fashion as to cause obstruction.

*Comment.* The connection between duodenum and colon had probably been present for some time prior to the patient's entrance to The Mount Sinai Hospital. The presence of the opening had never been suspected because the duodenal material was being drained directly into the colon. When the continuity of the large bowel was interrupted and a colostomy performed, the fistula immediately manifested itself by the appearance of excessive flow through the colostomy stoma.

It must also be assumed that the gradual deterioration of the patient may have been partly due to the fact that food was passing directly from the duodenum to the colon, thereby depriving the patient of necessary nutrition.

The presence of a fistula between duodenum and colon had not been suspected preoperatively because such a location had never been seen at this hospital and apparently had not been noted elsewhere either.

#### SUMMARY

A case of regional enteritis is presented in which there was a fistulous connection between duodenum and colon. The complication appears not to have been previously described.





*Charles A. Crosby*

## Dr. Charles A. Elsberg

August 24, 1871–March 18, 1948

Dr. Charles Albert Elsberg was born in New York City August 24, 1871, the son of Albert and Rebecca Elsberg. He had three brothers and a sister. He was graduated from the College of the City of New York in 1890, the college which so signally honored him in 1935 with the Townsend Harris Medal and again in 1947 with an honorary degree. In 1893 he graduated from the College of Physicians and Surgeons, Columbia University winning the Harsen Clinical Medal.

His professional life lends itself to a natural division into three periods. The first from 1893 to 1909 may be termed "Early Mount Sinai Days." During this time he served his internship at Mount Sinai, he studied abroad, he worked in the laboratory as assistant pathologist, he served his apprenticeship in surgery in the outpatient department and his early days on the general surgical service as adjunct surgeon. Toward the close of this period his interest in neurological surgery was becoming manifest.

The second period covers the years from 1909 to 1929. It begins with the founding of the Neurological Institute and ends with his separation from the Mount Sinai Hospital. It could well be termed the years of dual interests. It was during this period that he was made Associate Surgeon (1911) and Attending Surgeon (1914) at Mount Sinai while serving as Attending Surgeon to the Neurological Institute. While it marks the complete transition from general to neurological surgery, it is also the time when he was at his best as a skillful general surgeon. During the year 1924 through 1928 he was vice president of the New York Academy of Medicine.

The third period from 1929 to 1937, the closing years of his professional activity belong to the Neurological Institute and the College of Physicians and Surgeons. It was in 1929 that the new Neurological Institute opened its doors and closer physical relationship was established with the Medical School. He took an active part in planning the new building and especially the operating facilities. He often climbed in the unfinished structure to watch its progress.

The publications of Dr. Elsberg are made up of four books and five bound volumes of reprints. A glance at some of the titles in their chronological sequence will show into what period they fall. The first paper concerning the serum diagnosis of typhoid fever was written while he was assistant pathologist at Mount Sinai Hospital. The date places it within a year of Widal's publications on that subject.

An early paper (1901), which dealt with the pathology, diagnosis and treatment of subphrenic abscess, was an important contribution at that time. He published several papers on typhoid perforations. In 1909 he described a very ingenious cannula for artery to vein transfusions as it was done in those days. His interest in chest physiology led to the development of an intratracheal anesthesia machine.

His early experimental work dealt with thoracic physiology, the healing of heart wounds, the influence of posture on pneumothorax, and intratracheal anesthesia. Later on his investigations dealt with nerve regeneration and convulsions. Still later the physiology of smell and vision engaged his attention.

The earliest publication on a neurosurgical subject was in 1904 a report of two cases of cerebello-pontine angle tumor. There was then a lapse of five years before the next neurosurgical paper appeared.

In the second period the writings were almost exclusively on neurosurgical topics. As early as 1911 there was a report on 43 laminectomies. It was during this period that the books "Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes" (1916), and "Tumors of the Spinal Cord" (1925) were published. The other publications were in large part devoted to various aspects of spinal cord lesions and some well chosen contributions to the surgery of brain tumors.

During the early part of the third period he published a few papers on clinical neurosurgical subjects. Later in the period the greater part of his time and most of his writings dealt with the basic investigations of the senses of smell and vision, and with some practical applications of these studies. He was not too busy to devote time to the Bulletin of the Neurological Institute, serving as its editor for several years. In addition he carried on his teaching as Professor of neurological surgery at the College of Physicians and Surgeons.

In 1937 he retired from active hospital service and was made Director Emeritus at the Neurological Institute. The following year he served as president of the American Neurological Association and delivered the Charles K. Mills Lecture before that Society. In 1941 he brought up to date his experiences in spinal cord surgery in a book "Surgical Diseases of the Spinal Cord." In 1944 under the title of "The Story of a Hospital" he related the history of the Neurological Institute of New York in the organization and development of which he had played such an important part.

To have been an active general surgeon and then an equally busy neurological surgeon, to have served in two hospitals as head of surgical services, to have engaged in teaching and research, to have published some 150 medical articles and 4 books reveals one characteristic of Dr. Elsberg, his industry. It was practically a daily habit of his to leave his office in the very late afternoon with his briefcase filled with unfinished work, work to be completed in part before retiring, in part before breakfast after an early rising.

An accomplishment of his not so well known was his ability with pen and pencil. He could illustrate an operative procedure, or could and did correct illustrations made for him by artists.

Of him it may truly be said that he had but two real interests, his work and his family. His loyalty to these two was almost fierce in its intensity. Had a choice to be made between them his family would always have been first.

Outside of his family Dr. Elsberg had few intimates. While he was easy to approach, it was on a plane removed from the personal. He was at all times a

gentleman, as we understand it "a gentleman of the old school." He had considerable charm, and more than a touch of naiveté.

His ability to think clearly, logically and intensely helped him in the solution of many medical problems. This ability coupled with his attention to detail made him the acknowledged leader in and the outstanding contributor to the development of spinal cord surgery.

In 1937 Dr. Elsborg married Jane Stewart. This gave him during his sunset years a beautiful companionship which meant all the more to him because it came late in his life. Soon after marriage they moved to Stamford, Connecticut where he began to lessen his activities. Nevertheless, it was during this time that the history of the Neurological Institute was published. He enjoyed his country life and the peace it brought, unfortunately it was not to continue long enough.

In his last long drawn-out illness which ran the gamut from discomfort to severe pain he never lost his fortitude. As a physician he viewed himself objectively and drew upon a reserve of strength and courage beyond belief. He died March 18, 1948.

IRA COHEN



## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*A Device of Value for Roentgen Ray Epilation.* H. T. BEHRMAN AND O. L. LEVIN. Arch. Dermat. & Syph., 54: 200, August, 1946.

The performance of roentgen ray epilation for tinea capitis is a technic requiring experience and skill on the part of the dermatologist. Formerly this treatment consumed several hours of time to insure its accurate performance. However, with the addition of various time-saving methods over a period of years, the procedure can now be carried out in less than one hour. Any method which may lessen the technical difficulties or lead to greater accuracy of performance is deemed worthy of report. For several years, a device has been successfully employed in the dermatologic radiotherapy clinic of The Mount Sinai Hospital. It had been made in response to a request for some method which would lead to more accurate focusing of the roentgen rays on the five points of the Kienboeck-Adamson fields. Prior to this, intersecting silk threads had been placed over the cone in a not particularly satisfactory effort to find the center. With the present method, a wide cone with a focus-skin distance of 15 cm. if placed over the portal of an x-ray tube. The device is so constructed as to slide over this cone. It consists of a thin circular metal sheet of the same size as the cone. At the edges of this metal sheet is a blunt steel rod which extends downward for an additional 5 cm., thus increasing the focus-skin distance to 20 cm. The roentgen ray technic, accordingly, incorporates a focus-skin distance of 20 cm. among its other physical factors. In the actual performance of the epilation, the child is placed in the proper position and shielded with lead rubber. The device is placed on the cone. The flat surface of the device is then made parallel to the plane of the area of scalp under treatment, with the projecting rod touching the respective Kienboeck-Adamson points. The x-ray tube is then locked into position and the device gently removed from the cone. This procedure is repeated for each of the five fields. Other methods of improved fixation or centering of either the patient or the tube are in use, but this device has proved satisfactory during the performance of hundreds of roentgen-ray epilations. For this reason, we are describing its use, with the expectation that other dermatologists may find it of value.

*Pneumothorax Therapy for Early Bronchiectasis.* H. HENNEL. J. Thoracic Surg., 15: 239, August, 1946.

A group of cases of early bronchiectasis is presented in which pneumothorax therapy was instituted after a two to four months trial of the usual therapeutic measures (including sulfonamides, bronchoscopic aspiration, partial drainage, etc.) failed to arrest the progressive course of the disease. The mechanism by which bronchiectasis develops is discussed, and the importance of atelectasis is emphasized in that connection. Pneumothorax therapy produced a prompt and lasting clinical cure in all 6 cases in which it was tried. The mechanism by which pneumothorax produced this favorable result is discussed in detail. The probable value of pneumothorax therapy in preventing the development of bronchiectasis in cases of protracted suppurative bronchopneumonia is discussed and illustrated. It is concluded that pneumothorax therapy should receive first consideration in cases of early bronchiectasis and that radical surgical measures should be employed in such cases only when pneumothorax fails to produce the desired results after a short trial.

*Animal Operating Equipment for Experimental Ocular Surgery.* H. M. KATZIN. Arch. Ophth., 36: 215, August, 1946.

Animal operating equipment and the methods used for experimental ocular surgery on the rabbit are presented. The equipment described has been used in hundreds of operations and has been entirely satisfactory in his hands.

*The Regression of Psychiatry in the Army.* W. NEEDLES. Psychiatry, 9: 167, August, 1946.

This report on military psychiatry differs with the eulogistic reports which have found their way into the professional and popular journals. The author submits that military psychiatry, at least as practiced in one of the largest theaters of operation, ignored and neglected psychiatric fundamentals and, to that extent, regressed and deteriorated. The authoritarian psychiatrist with a naive psychologic outlook might feel at home in this mental climate but the enlightened psychiatrist often found himself hard put in his task of protecting the interests of the army, on the one hand, and of the sick soldier, on the other, without doing violence to psychiatric truth in the process. The author utilizes a series of concrete situations, which presented focal points of disagreement between the authoritarian and enlightened psychiatrist, to point up their respective attitudes and methods of dealing with certain problems. He offers several suggestions for liberalizing and improving military psychiatry.

*Ring Scotoma and Tubular Fields. Their Significance in Cases of Head Injury.* M. B. BENDER AND H. L. TEUBER. Arch. Neurol. & Psychiat., 56: 300, September, 1946.

After injury to the brain, apparent ring scotomas, concentric contraction of visual fields, shifting and "spiral" fields may be found with specific methods of examination of the fields. Different types of fields may be encountered in one and the same case. However, the changes observed vary consistently and directly with the different methods of plotting. This is illustrated in a case which was studied with neurologic, psychophysiologic and phenomenologic methods. The unusual field changes (viz., ring scotomas and contracted and spiral fields), as well as severe disturbances in visual perception (haziness, fragmentation and obliteration of images from the periphery inward), seemed to be produced by a continual fluctuation in the visual threshold for different parts of the field, with concomitant phenomena of extinction. It is concluded that such ring scotomas, despite their variability, have an "organic" basis, as pointed out by Goldstein in 1927.

*The Clinical Evolution of Vascular Damage in Diabetes Mellitus.* H. DOLGER. Bull. New York Acad. Med., 22: 482, September, 1946.

In 200 patients below 50 years of age, careful repeated examinations of the eye grounds, blood pressure, and urine for albumin revealed no single instance where the diabetes had lasted 25 years in which the patient escaped the development of vascular damage. Some presented rapid progression into the full blown clinical syndrome of intercapillary glomerulosclerosis frequently with blindness. In the majority, however, the lesions progressed slowly with accelerated damage occasionally in isolated viscera and tissues such as renal, coronary and cerebral vessels, etc. In the middle age groups, the damage often appeared within five years of the onset of diabetes and not infrequently was noted coincidental with the onset. In a few instances, the lesion seemed to antedate the onset of clinically detectable diabetes. Retinal hemorrhage was the predominant lesion when diligent search was made routinely, and it often preceded the appearance of albuminuria and/or hypertension. When this sequence was not observed it could probably be attributed to failure to notice transient hemorrhages which had resolved in the interval between examinations. All three lesions appeared in the patients regardless of the age of onset or degree of severity of the diabetes, the need for insulin, the type of diabetic "control" or diet employed, the blood cholesterol levels, or the absence of x-ray evidence of arterial calcification. The triad of retinopathy, hypertension, and albuminuria is more than a terminal "pathological" syndrome.

*The Association of Hypernephroma with Amyloidosis of the Kidney.* A. HYMAN AND H. E. LEITER. *J. Urol.*, 56: 303, September, 1946.

Four cases of amyloid disease associated with hypernephroma of the kidney are presented. The diagnosis of this syndrome can be made clinically. One case is recorded that failed to improve postoperatively by the use of liver extract and vitamins.

*Hepatic Insufficiency. I. Pathophysiology and Clinical Aspects.* S. S. LICHTMAN. *Ann. Int. Med.*, 25: 453, September, 1946.

This is the first of a triad of papers based on lectures on various laboratory and clinical aspects of hepatic failure. The proper choice of liver function test entails familiarity with the types and grades of progressive liver failure. The clinical aspects are integrated with the shifting level of insufficiency. Thus, the clinical observer is better prepared to test prevailing functional circumstances, evaluate prognosis, and treat adequately. The types of failure are parenchymal, circulatory, biliary or mixed forms; the grades are minor, moderate, and severe. The individual functions failing at different levels of insufficiency are tabulated. The pathologic physiologic background of the common symptoms and signs of liver disease is developed.

*Differences in Excretion of Hippuric Acid and Glucuronates after Ingestion of Sodium Benzoate and Benzoic Acid.* I. SNAPPER, E. GREENSPAN AND A. SALTZMAN. *Am. J. Digest. Dis.*, 13: 275, September, 1946.

After ingestion of 5.8 grams of sodium benzoate the first 2-hour specimen usually contains more hippuric acid than the second. In the third 2-hour specimen the hippuric acid content is usually small. After ingestion of 5 grams of benzoic acid the first 2-hour specimen contains never more—usually less—hippuric acid than the second. The third 2-hour specimen usually contains a considerable amount of hippuric acid. Individuals excrete more hippuric acid during the first two hours after the ingestion of 5.8 grams of sodium benzoate than in the first two hours after ingestion of 5 grams of benzoic acid. This pattern of hippuric acid excretion indicates that the absorption of benzoic acid is slower than that of sodium benzoate. After ingestion of 5.8 grams of sodium benzoate the first 2-hour specimen shows strong glucuronic acid reactions; in the second 2-hour specimen the glucuronic acid reaction is usually appreciable; in the third specimen the reaction is negative. After ingestion of 5 grams of benzoic acid the glucuronic acid reaction is always negative in the first and third 2-hour specimens. Only rarely is an appreciable reaction found in the second 2-hour specimen. If 5.8 grams of sodium benzoate are administered in nine doses at half-hour intervals no excretion of glucuronic acid is observed. These observations relate only to individuals with normal liver function.

*Neurodermatitis and Occupational Dermatitis.* H. T. BEHRMAN AND O. L. LEVIN. *New York J. Med.*, 46: 2160, October, 1946.

Occupational disease may be defined as a disease arising out of, or in the course of work or occupation. This very broad definition adequately covers the majority of conditions of industrial origin, but is responsible for numerous borderline problems in the field of dermatology. Inasmuch as almost 60 per cent of all occupational disease is related to the skin, this problem is a very serious one. In recent years there has been an increasing tendency among dermatologists to accept psychogenic factors as causative agents in the production of dermatoses. Numerous emotional impulses arising in the cerebrum are able to produce changes in the functions of the internal organs as well as in the skin. Cutaneous symptoms may be present without any recognizable internal disorder. Pruritus may be a most annoying symptom unaccompanied by structural changes in the skin. The purpose of this report is to note that several cases of ordinary occupational or contact dermatitis of the hands were either associated with, or followed by an eruption of the antecubital spaces and neck clinically typical of neurodermatitis.

*Nutritional Amblyopia in American Prisoners of War Liberated from the Japanese.* S. M. BLOOM, E. H. MERZ AND W. W. TAYLOR. *Am. J. Ophth.*, 29: 1248, October, 1946.

The early eye findings in American soldiers while in Japanese prison camps and residual findings in some of these men after liberation have been presented. The following conclusions are drawn: Malnutrition due to a deficient diet can cause an optic atrophy manifested by defective vision, central or centrocecal scotomas, and pallor of the nerve head. The deficiency seems to be due to a lack of vitamin B<sub>12</sub>, since the diet, in every case was highly deficient in this vitamin; the symptoms occurred coincidentally with beriberi; and the symptoms were relieved by thiamin when administered in the early stages of the deficiency. If treatment is not instituted early enough, the condition becomes irreversible, as witnessed by the lack of improvement after administration of intensive vitamin therapy at this Center. The loss of vision and the size of the central scotomas were not in direct proportion to the amount of optic atrophy seen. The appearance of the disc varied from minimal to complete atrophy, with the vast majority of eyes showing mild temporal pallor. The maculas had a normal appearance in 60 per cent of the cases and a mottled appearance with loss of the foveal reflex in the remainder. The nerve involvements—peripheral neuritis and optic atrophy—were the only residual abnormal findings made at this Center on patients who had suffered severe malnutrition over a period of years.

*The Treatment of Postoperative Biliary Dyskinesia.* R. COLP. *Gastroenterology*, 7: 414, October, 1946.

All cases have been followed for from two to eight years. Six cases have shown definite improvement and have been relieved of their troublesome symptoms. One patient has had occasional slight epigastric distress during her menstrual period while another has had definite recurrence of colic after nineteen months of absolute freedom from attacks. Surgical section of the sphincter usually causes permanent paralysis. Because of a definite recurrence of symptoms in one case, it may be advisable in the future to divide the sphincter in two separate planes. Evidently the scar resulting from the sphincterotomy has never caused a secondary contraction of the papulla resulting in stenosis and biliary stasis.

*The Relationship of Trauma to the Perforation of Peptic Ulcer.* B. B. CROHN, M. O. ROUSE AND H. W. SMITH. *Gastroenterol.*, 7: 4, October, 1946.

Although the greatest number of perforations occur post-prandial, after drinking carbonated beverages, or during any of the activities of work or daily physical exertion, trauma is an accepted cause of perforation or of hastening one. The courts, however, interpret traumalously and accept as such physical exertion incident to a days activities interpreted as greater than mild. The Liniger and Molineux postulates for trauma as the cause of peptic ulcer, are generally accepted and with modification can apply to trauma as the cause of perforation. 1. Trauma must be severe. 2. Symptoms follow the injury immediately. 3. The symptoms must characterize the disease. However, the latent period between the perforation and the manifestation of the symptoms of perforation may be prolonged. This silent phase makes great difficulty in associating the onset of the acute phase with an every day act. In spite of this the State Workmen's Compensation Board recognizes unusual exertion as true trauma and compensable. In general direct and sufficient trauma, wound or bodily injury, is conceded by most authorities to be the etiology of ulcer perforations. The point where unusual and extra heavy exertion becomes trauma needs scientific and judicial discrimination.

*Atresia and Stenosis of the Aqueduct of Sylvius.* J. H. GLOBUS AND P. BERGMAN. *J. Neuro-path & Exper. Neurol.*, 5: 342, October, 1946.

A review of the literature concerning the pathogenesis of atresia and stenosis of the aqueduct of Sylvius offers no impressive evidence that inflammation, toxic agents or trauma are etiologic factors. Embryological studies of the developing midbrain have disclosed



fairly constant alterations occurring in and about the aqueductal region. These consist primarily of the appearance and disappearance of the ependymal folds, which leave subependymal residues, and a loss of ependymal lining in certain parts of the embryonic mid-brain vesicle, forming a site for glial protrusions. Six previously reported and three new cases of atresia are investigated in the light of these findings, and the probability is considered that the defect of the aqueduct is a blastomatous process, congenital in origin, frequently associated with coexistent anomalies.

*Proctalgiias and Allied Non-Inflammatory Perianal Dyscrasias: Coccygodynia Proctalgia Fugax, Neurogenic Pruritus Ani.* E. GRANET. *Am. J. Digest. Dis.*, 13: 330, October, 1946.

Several syndromes not of neoplastic or inflammatory origin, each of which causes pain or other discomfort in the perineal, anal, or rectal regions are presented as to etiology, pathological physiology and management. The relationship of coccygodynia to spastic contraction of the muscles attached to the coccyx, and in some instances to a bursitis involving these muscles is discussed. Simple treatment by massage of the spastic muscles according to the method of Thiele results in rapid relief of pain with ensuing muscle relaxation. The syndrome described as Proctalgia Fugax is difficult to study. Attacks of pain are sudden, occurring frequently with no prodromal symptoms and awakening the patient out of sleep. Severe spasm in the region of the recto-sigmoidal junction is suggested as the cause of the pain, and its psychosomatic nature seems well-established. Glyceryl trinitrate or similar rapidly acting antispasmodics may prove effective in therapy. Chronic recurrent anal pruritus occurring in individuals with definitely established personality difficulties, the perianal skin of whom retains its relatively normal characteristics must be classified as neurogenic in origin. In these patients all local therapy affords no relief of symptoms. In the recent literature, numerous reports by both psychiatrists and dermatologists are quoted to demonstrate the "pleasure-pain" principle and its relationship to pruritus. The masturbatory element is illustrated by the mechanism of rubbing or scratching while the masochistic element is inherent in the concomitant suffering. Cases of neurogenic pruritus are not obscure, must be recognized early and adequate psychotherapy instituted. Local treatment is futile in these patients.

*Apical Systolic Murmurs in Incipient Rheumatic Heart Disease.* A. M. MASTER. *Bull. New York Acad. Med.*, 22: 535, October, 1946.

Certain difficulties are encountered in evaluating apical systolic murmurs; i.e., murmurs vary; they appear and disappear and apparently often regress completely; a history of rheumatic fever may not be obtained in half the cases of organic valvular disease; the problem of differential diagnosis is ever present. The very appreciation of these difficulties facilitates interpretation of the murmur. A careful physical examination may uncover physical qualities of the murmur in addition to its loudness, which add to its significance. A loud first sound at the apex, a loud second pulmonic sound, a holo-systolic murmur, a "musical" murmur, a "harsh" murmur, a "sea gull" murmur, a "constant" murmur, all lend importance. Repeated examination, in many positions, and after exercise may be necessary. Furthermore, a diastolic murmur may be discovered. The x-ray film and fluoroscopic examination help in revealing a straightened left border of the heart and, more particularly, filling in by the left auricle of the space under the left main bronchus. This is an early sign of left auricular enlargement and appears long before the esophagus becomes indented or the left auricle moves to the right side of the heart. In differential diagnosis, the important conditions to bear constantly in mind are (1) effort syndrome or neurocirculatory asthenia (the "Small" heart syndrome), (2) the funnel-shaped and the flat chest, and (3) a split first sound. One must also think of hypertension, hyperthyroidism, and anemia in the differential diagnosis.

*Electrophoresis in Medicine.* K. G. STERN AND M. REINER. *Yale J. Biol. & Med.*, 19: 67, October, 1946.

This is a review of electrophoretic studies of predominantly medical interest on normal

and pathological blood serum, plasma, isolated proteins and body fluids, with an attempt to correlate changes observed in the electrophoretic patterns with the physiological state of the organism. The protein spectrum in plasma and serum is the resultant of a host of factors concerned with the formation, the interaction and the destruction of the individual components. A close correspondence exists between the blood, the protein system and the physiological state of the individual as a whole, rather than a given pathological condition.

*Prescription Writing by the Dentist.* L. STERN, JR. New York J. Dent., 16: 301, October, 1946.

Progressive practice in dentistry and oral surgery includes the responsibility of prescribing therapeutic agents for the relief of pain, control of infection, and management of emergencies. The situations in which the dentist may benefit his patient by the intelligent administration of drugs is reviewed. Particular reference is made to the prescription of penicillin, morphine derivatives, salicylates, barbiturates, vitamins, and in a crisis, cardiac or central nervous stimulants.

*The Usefulness of the Cornell Selectee Index at the Neuropsychiatric Unit of a Naval Training Center.* H. I. WEINSTOCK. U. S. Nav. M. Bull., 46: 1583, October, 1946.

The total score of the Cornell Selectee Index contributes almost nothing to identification of men discharged at a naval training center for neuropsychiatric reasons. The value of "stop" questions, the necessity for greater honesty, and the need to avoid dichotomy of two possible answers lead to the decision that it would be advisable to use, instead of the Cornell Selectee Index, a list of "stop" items drawn from this and other sources and framed to allow gradations of severity.

*Principles and Practice of Aerosol Therapy of the Lungs and Bronchi.* H. A. ABRAMSON. Ann. Allergy, 4: 440, November, 1946.

Penicillin aerosol therapy of the lungs was initiated and organized for the Technical Division, Chemical Warfare Service, by the writer in collaboration with the Maey Foundation and other agencies. The relationship of aerosols to general problems in the Chemical Warfare Service is discussed. Definitions of aerosol, atomization, nebulization, vaporization and aerosolization are considered. Large particle atomization and small particle nebulization are described in detail. It is shown on the basis of the study of particle size distribution by radius and by weight that rebreathing is inefficient and not desirable. Simple apparatus is described which is inexpensive and which can be used for all routine antibiotic aerosol therapy of the lungs. The clinical application of aerosol therapy is considered from the point of view of the use of epinephrine, penicillin, streptomycin, sulfonamide and hydrogen peroxide aerosols. Preliminary data are discussed on the use of antibiotic and hydrogen peroxide aerosols in the treatment of secondary infection in pulmonary tuberculosis. The difficulties of using hydrogen peroxide are stressed because of the presence of catalase in the sputum. It is believed that in the presence of a suitable anticatalase, hydrogen peroxide aerosol will become one of the most efficient antibiotic substances for pulmonary therapy.

*Influence of Liver L. Casei Factor on Spontaneous Breast Cancer in Mice.* R. LEWISOHN, C. LEUCHTENBERGER, R. LEUCHTENBERGER AND J. C. KERESZTESY. Science, 104: 436, November, 1946.

In contrast to the effect of the crystalline fermentation L. Casei factor previously reported, the intravenous injections of the Liver L. Casei factor into mice bearing spontaneous mammary carcinomas at doses of 5 and 100 micrograms did not lead to regressions of these tumors. Intravenous injections of 5 micrograms of the Liver L. Casei factor increased the incidence of lung metastases when compared with untreated controls. Intravenous injections of 100 micrograms of the Liver L. Casei factor decreased the life span from seventy-four to fifty-five days, probably due to the increased growth of the primary tumors.

*Pathogenesis of Cirrhosis of the Liver Occurring in Patients with Diffuse Toxic Goiter.* E. MOSCHOWITZ. Arch. Int. Med., 78: 497, November, 1946.

A type of hepatic cirrhosis apparently pathognomonic of diffuse toxic goiter was found in 10 of 31 cases. The lesion is identical in both form and progression with that seen in chronic hepatic venous congestion and cardiac cirrhosis but differs from the latter in that topographically it is not around the central veins but in the interlobular septums, often encroaching on the lobule itself. In the early phases the areas of fibrosis can be traced to the terminal ramifications of the hepatic artery as it passes into the interlobular vascular septa. This artery and its ramifications represent a significant factor of the equalization of intravascular pressures between the hepatic artery and the portal vein within the liver. Pathogenetically the lesion is the consequence of the increased velocity of blood flow, an invariable accompaniment of, and almost peculiar to, this disease in the early phases. The increased velocity is associated with increased blood volume and increased blood flow. These altered circulatory dynamics render the maintenance of the normal pressure relations between the hepatic artery and the portal vein difficult; eventually decompensation arises, with resulting stasis in these areas, and the lesion begins as capillary congestion. In time, just as in chronic venous congestion of central origin, capillary sclerosis results, with eventual fibrosis. In this conception, the cirrhosis of diffuse toxic goiter is the consequence of forward failure, while that of chronic hepatic venous congestion is the result of backward failure. The cirrhosis is distinguished by the fact that it is predominantly in the subcapsular zone of the liver. Evidence is submitted that, as in the ordinary congestive liver, this is due to the resistance offered by the capsule of the liver. The cirrhosis also possesses the peculiarity that it arises only from the smaller subdivisions of the portal spaces. This is because the interlobular branches of the hepatic artery arise only from such spaces. The cirrhosis bears a definite but not absolute relation to the duration of the malady, which is what one might expect from the pathogenesis. Nevertheless, this cirrhosis is sometimes absent in persons who submit a history of apparent long duration of the disease. This may be accounted for by the observation that chronic venous congestion is an exceedingly common sequence of long-standing diffuse toxic goiter, even in patients without cirrhosis, and that this venous congestion neutralizes the increased velocity of blood flow.

*Alterations in Pathogenesis of Experimental Lymphocytic Choriomeningitis Caused by Pre-passage of the Virus through Heterologous Host.* G. SHWARTZMAN. J. Immunol. 54: 293, November, 1946.

Three strains of the virus of lymphocytic choriomeningitis were maintained by serial passages through mice and guinea-pigs. The substrains thus obtained possessed marked meningo-encephalotropism but differed in viscerotropic affinities. The meningo-encephalotropism was maintained by both species. Viscerotropism was lost in the mouse, but restored or imparted to the virus by the guinea-pig. Significant alterations in the pathogenesis of experimental disease were contingent upon the differences in viscerotropic affinities of the substrains.

*Increased Excretion of Glucuronates After Ingestion of Benzoic Acid by Patients with Damaged Liver.* I. SNAPPER, A. SALTZMAN AND E. GREENSPAN. Am. J. Digest. Dis., 13: 341, November, 1946.

After ingestion of 5 grams of benzoic acid by patients with liver cirrhosis or hepatitis the glucuronate reactions are always positive in the second 2 hours urine specimen, usually also in the first and third 2 hours' specimen. This glucuronate excretion is a sensitive liver function test. If after ingestion of 5 grams of benzoic acid, none of the three two-hours specimens shows a positive glucuronate reaction, serious liver damage as accompanies hepatitis or cirrhosis is not present. The increased glucuronate excretion after ingestion of benzoic acid by patients with a damaged liver depends on the impairment of the hippuric acid synthesis in the damaged liver. This leads to the presence of large quantities of free benzoate in the damaged liver which is conjugated with glucuronic acid.



*On the Influence of Stilbamidine upon Myeloma Cells.* I. SNAPPER AND B. SCHNEID. Blood, 1: 534, November, 1946.

Injections of stilbamidine cause morphological changes in myeloma cells. During this treatment large basophilic granules appear in the cytoplasm which show a tendency to become confluent. These granules stain red with pyronine and can be visualized in the supravital stain with neutral red. One of the main constituents of these inclusions consists of ribose nucleic acid. These morphological changes seem to be limited to myeloma cells, since in none of the other bone marrow elements do comparable granules or inclusions develop.

*Colonic and Proctoscopic Diseases.* R. TURELL. Surg., Gynec. & Obst., 83:417, November, 1946.

The author presents an extensive review of the literature dealing with colonic and rectal diseases. In this article, part I of the review is published. The following subjects are discussed: chemotherapy, anatomic considerations, congenital lesions, inflammatory lesions of the colon and neoplastic disease, benign and malignant.

*Distribution of Alkaline Phosphatase in the Human Liver.* M. WACHSTEIN AND F. G. ZAK. Arch. Path., 42: 501, November, 1946.

Alkaline phosphatase activity was studied in sections of livers of human post mortem material. A fairly regular distribution was found in livers from patients who had died from various diseases not involving the liver itself. Considerable increase of enzymatic activity was seen in bile capillaries in the livers of several of the patients having obstructive jaundice. Increased activity was also seen in the bile capillaries in some of the livers with hepatocellular damage. Necrotic liver cells showed no significant increase of enzymatic activity. Considerable activity was seen in the proliferating connective tissue in livers of patients with subacute hepatitis and patients with toxic cirrhosis and in the livers of some of the patients with Laennec's cirrhosis. Metastatic as well as primary tumor tissue showed moderate phosphatase activity of the nuclei. Infiltrating leukemic cells showed some phosphatase activity of the nuclei. Infiltrating leukemic cells also showed some nuclear phosphatase activity. In some of the livers which were not involved primarily by diseases, considerable increases of cytoplasmic phosphatase activity occurred. The behavior of phosphatase revealed in these sections favors the assumption that the increase of serum alkaline phosphatase in cases of damage of the liver is due to retention of the enzyme in the blood. The inability of the liver to excrete it may be caused by external obstruction or by cellular dysfunction. The importance of extra-hepatic factors, however, should not be underestimated.

*Diffuse Vascular Diseases.* G. BAEHR. Modern Concepts of Cardiovascular Disease. Am. Heart Assn., 15: 12, December, 1946.

The author divides the discussion of the so-called "diffuse vascular diseases" into two parts. In the first he describes fibrinoid degeneration and diffuse collagen disease and their appearance in allergy and serum sickness, periarteritis nodosa, thrombo-angiitis-obliterans and rheumatic fever. Despite the connective tissue changes observed in all these diseases, the distribution as well as the type of fibroplastic alterations may vary widely. The reaction may be degenerative, sclerotic or cellular, or there may be variable combinations of these processes. Whereas in some conditions the fibrinoid reaction may be seen in the tissues and organs (e.g. lupus erythematosus and diffuse scleroderma), in others (e.g. thrombo-angiitis-obliterans periarteritis nodosa, and rheumatic fever) it may be limited to the walls of the blood vessels. Although similar connective tissue changes with a fibrinoid reaction, have been seen experimentally and clinically in allergy, the relationship of this group of diseases to hypersensitiveness has by no means been proven. The fibrinoid degeneration of collagen is seen in a variety of conditions (e.g. in malignant hypertension, the Goldblatt experiment, at the base of peptic ulcers and adjacent to foreign bodies) which are not even



remotely related to allergy. Periarthritis nodosa with its many allergic manifestations, including eosinophilia, suggests that the fibrinoid degeneration in the arteries is due to hypersensitiveness. In thrombo-angiitis the affected tissues of the walls of the diseased vessels may show fibrinoid degeneration and it would appear that the relationship, perhaps allergic, to tobacco, is fairly clear. In rheumatic fever the fibrinoid degeneration with cellular response (Aschoff bodies) and the production of new fibrous tissue, especially in the cardiac valves, is observed. The evidence that rheumatic fever represents an allergic response to hemolytic throat infections, though widely held, is by no means conclusive and the rise in the streptolysin titer is not specific. There is considerable evidence that rheumatic fever resembles a true infection.

The paper's second part is devoted to a discussion of the clinical and pathological characteristics of disseminated lupus erythematosus and diffuse scleroderma. The systemic, cutaneous, muscular and serous distribution of lupus erythematosus are considered. Fibrinoid degeneration of the connective tissue is more diffusely distributed with little cellular reaction, with involvement of the walls of small arteries, the subendothelial layer of the glomerular capillaries and the subendothelial connective tissue of the endocardium, epicardium and other serous membranes. Involvement of the basement membrane of the glomerular capillaries leads to the "wire loop" appearance. Vascular occlusion as the end stage of swollen collagenous material in the media and intima of the lumens of small arteries may appear. Fibrinoid degeneration may also occur in the subendothelial connective tissue of the pericardium producing pericarditis, the pleura with pleuritis, the peritoneum with perisplenitis or perihepatitis, and the endocardium and valves with extrusion above the surface and the formation of coarse verrucae (Libman-Sacks form of endocarditis). The verrucae are free of bacteria, except in the terminal stages and no Aschoff bodies are found in the myocardium. Unlike rheumatic fever, murmurs are rarely heard, the electrocardiogram is usually normal, leucopenia is common and lymphadenopathy is frequent. The vascular lesions of lupus erythematosus are not invariably present at any one stage of the disease and patients may die after a short fulminating illness in a profound toxic state with little microscopic change at post mortem. There is no evidence to support an allergic theory for the disease, and despite its preponderance among young females, there is no evidence of an endocrine factor. Although the connective tissue changes in the viscera in diffuse scleroderma are identical in distribution and in type with those in disseminated lupus erythematosus, the pathological changes in the skin and esophagus are quite different. The cutaneous manifestations begin in the periphery, as in lupus erythematosus, but the subcutaneous tissue undergoes dense sclerosis with thickening of the skin of the nose, cheeks, forehead, etc., and consequent stiffness and contractures of the fingers, etc. Immobilization and secondary sclerosis of the vessels may result in bony rarefaction, degeneration of the joint capsules and may lead to large periarticular calcific masses. The clinical course is usually afebrile, is slow, so that death may occur after many years from progressive debility or from dysphagia due to sclerotic changes in the esophagus. Arrests and remissions are not uncommon. Collagenous degeneration of the subendothelial connective tissue may produce attacks of pericarditis and pleuritis, and changes in the renal arterioles may cause microscopic hematuria. Scleroderma may at times follow in the wake of Raynaud's phenomenon. Extensive skin pigmentation may require differentiation from Addison's disease. The predominant pathologic characteristic is the dense sclerotic process in the involved areas. The spleen is the only organ in lupus erythematosus where sclerosis may be pronounced. In spite of the similar collagenous change in the two diseases there is no clinical resemblance nor is the female sex predominance found in scleroderma. All of the diseases discussed in both parts of the paper, provide evidence of the systemic distribution of fibrinoid degeneration which is not specific for allergic or hyperergic states. The widely distributed lesions in both latter diseases represent a diffuse injury of still unknown nature to the supporting and binding substance of all the organs and tissues of the body through which the humoral and metabolic exchange between the blood and other tissues takes place.

*The Next Ten Years in Medicine. Prospects in Science, Education and Practice.* G. BAHR. New York Med., 2: 24, December, 1946.

Extraordinary changes in medicine are envisioned by the author. The recent advances in enzyme chemistry, which may ultimately aid in the victory over the cancer cell have been supplemented by the growing importance of research in physics; the establishment of a department of physics with a full time physicist in general hospitals will, it is felt, become a reality. This should stimulate the extension of use of electrotonic devices and radioactive isotopes and it is almost safe to predict that the products of atomic fission may revolutionize all branches of medicine. The field for clinical research in biophysics will be almost boundless. Rapid advances in virology will, it is believed, be stimulated by increased laboratory facilities. The widening gap between the complete general hospital and the smaller institution may be solved by a close functional affiliation between community hospitals, regional hospitals and medical centers both for the purpose of maintaining high standards of medical care as well as furnishing facilities for post-graduate instruction. The appointment of full time clinical chiefs in several large hospitals has been a distinct stimulus to the education of internes and residents. The expanded teaching program thus permits not only the enlargement of the clinical staff but greater opportunities, both clinical and laboratory, are thus afforded to the young qualified physician. The badly neglected field of social pathology and means of awakening social consciousness in physicians is emphasized. In practice, two major problems of preventive medicine are: 1) the recognition and, as far as possible, the correction of the social and environmental factors responsible for mental and physical illness and 2) the recognition of the earliest manifestations of such illness at a stage when it can still be cured or its progress arrested. Experiments in group medical practice through a program of voluntary medical insurance with part and even full time participants gives hope of improving preventive and therapeutic care to a large segment of the population and deserves a sympathetic attitude from the County Medical Societies. Such experiments present valuable educational and financial possibilities for the young physician, and should be both encouraged and adequately supervised by the County Societies.

*Staphylococcic (Suppurative) Pneumonia in Infancy and in Childhood and Its Surgical Aspects.* S. BLUMENTHAL AND H. NEUHOF. Am. J. Dis. Child. 72:691, December, 1946

Pneumonia due to the staphylococcus and occurring in infancy and childhood is of the suppurative variety. Proved cases are reported infrequently, but the disease probably is far from rare. The description of the clinical entity given here is based on the study of more than 40 proved cases. A concept of the pathogenesis of the disease and its classification into a number of types are proposed. The pathologic and clinical manifestations of the various types, with illustrative case reports are described. Emphasis is placed on certain roentgenographic features which when present are deemed to be characteristic or at times pathognomonic, of the disease. Until the advent of penicillin, staphylococcic pneumonia, often characterized by high mortality, was in the group of self-limited diseases influenced slightly, if at all, by drug therapy. Evidence points to penicillin as a drug which at times exerts a specific effect on the disease. The etiologic importance of a particular staphylococcus in pneumonias of early infancy and the likelihood that any pneumonic lesion in a young infant is of staphylococcic origin are emphasized. The clinical manifestations are stressed, so that the diagnosis can be suspected early in the disease, at which time penicillin therapy is most effective. The surgical complications of staphylococcic pneumonia are described. Timely surgical intervention for pleural complications can be life saving, particularly in cases of rapid accumulation of pus, with or without the addition of air. Closed drainage is advocated for such cases and temporizing methods are deplored. Attempts at sterilization of the infection by penicillin are not advocated, because only unsatisfactory results have been noted in limited personal experiences. If local administration of penicillin for empyema is to be employed, it should be reserved for patients who are not suffering from severe toxemia and/or the mechanical effects of mediastinal

displacement. Staphylococcal pulmonary abscess, to be anticipated rarely in the era of penicillin, is amenable to cure by correctly planned surgical drainage through visceroparietal pleural adhesions.

*Acute Encephalo-Meningo-Myelitis with Spastic Paraplegia in a Young Boy.* A. BRISKIER. J. Nerv. & Ment. Dis., 104: 599, December, 1946.

A case of a meningo-encephalo-myelitis with spastic paraplegia in a 14-year-old boy, characterized by a sudden onset, a dramatic course and a complete recovery is presented. The reason for describing the case is twofold: (1) that this type of myelitis may have a good prognosis and the patient should not be neglected despite the usual poor outcome; (2) that, since there is no specific therapy, the patient should have the benefit of the doubt and profit by hyperthermia through sulphur injections.

*The Influence of Barbiturate on Various Forms of Nystagmus.* M. B. BENDER AND F. H. O'BRIEN. Am. J. Ophth., 29: 1541, December, 1946.

Intravenous injections of barbiturate (sodium amytal 0.5 gm.) produces in the normal individual: (a) coarse nystagmus and inability to maintain gaze on voluntary deviation of the eyes in any one direction, and (b) abolition of opticomotor nystagmus as elicited by rotation of a striped drum upon which the patient fixates. Intravenous injection of barbiturate also alters or decreases the nystagmus due to disease of the brain stem and abolishes such types of nystagmus as: (a) latent (nystagmus obtained with monocular fixation or on exposure to darkness), (b) positional (nystagmus obtained on retraction of the head), (c) voluntary (nystagmus obtained by the patient at will), and (d) various forms of so-called congenital nystagmus. Intravenous injection of barbiturate restored eye movements in patients with hysterical ocular palsies and temporarily corrected an ocular squint of unknown origin. It is suggested that barbiturate in mild doses interferes with ability to control eye movements and ocular fixation by its action on the cerebral cortex, brain stem, and intermediate neuronal structures. Eye movements which do not necessarily involve a cortical component might be altered by barbiturate as a result of its action on the brain stem.

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*THE WILLIAM HENRY WELCH LECTURES*  
ESSENTIAL METABOLITES AND ANTI-METABOLITES<sup>1</sup>

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The topic of essential metabolites and anti-metabolites is part of the much wider subject of biological antagonisms between structurally related compounds, many examples of which are to be found in the literature of pharmacology. In many of these cases, however, little if anything is known about the modes of action of the antagonistic substances considered at the biochemical level. That is to say, little is known of the biochemical means whereby the antagonistic substances produce, respectively, their physiological effects and the corresponding nullifications of them. In the case of the so-called essential metabolites and their corresponding anti-metabolites, however, there does exist rather more detailed information about the biochemistry of the action of the growth-stimulatory substances themselves, and also about the mode of action, again at a biochemical level, of the corresponding anti-metabolites. Since the discovery of the antagonistic relationship between *p*-aminobenzoic acid and the sulphanilyl group of antibacterial substances, a very great amount of work has been devoted to the preparation and study of hundreds of compounds related in chemical structure to one or other of the known essential metabolites, with the object of finding therapeutically useful antibacterial and other substances. Up to the present the harvest, outside the sulphanilyl group, has been meagre, but only when considered from the viewpoint of obtaining therapeutically useful substances. But if considered from a somewhat wider viewpoint it may fairly be said that the discovery of the *p*-aminobenzoic acid-sulphanilamide relationship has stimulated lines of research which have already yielded and will continue to yield information about the intimate physiological chemistry of many different types of organisms. This cannot, in the long run, fail to help in the discovery of new and better chemotherapeutic agents. For the present purpose essential metabolites and anti-metabolites will be discussed in connexion with the growth of micro-organisms and the inhibition of their growth in culture. Discussion will be excluded of possible therapeutic use, where the therapeutic agent has to show a differential inhibitory effect, namely against the infecting organism and not, or only to a limited extent, against the host organism.

Some consideration may first be given to the implications which underlie the use of the phrase "essential metabolite," and its antithesis the phrase "anti-

<sup>1</sup> Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, on January 6, 1948.

<sup>2</sup> Visiting Commonwealth Professor in College of Medicine, New York University, October 1947-January 1948.

metabolite." In doing so, it is hoped to show that this formal antithesis is really an over-simplification of the real situations as they occur in nature. This rigid antithesis of metabolite and anti-metabolite does not reflect the true biological situation, and this recognition may perhaps be an initial step in making the most fruitful use of the conceptions involved. First, it may be well to consider the connotations of the phrase "essential metabolite," which was first suggested by Sir Paul Fildes in 1940 (9). The conception of essential metabolite derives to a large extent from studies of the nutritional requirements of micro-organisms. Taken as a whole, micro-organisms exhibit the very widest range of metabolic types: indeed, among them can be found examples showing the basal metabolic characters of almost every other type of organism, extending from the green plants to higher animals. The differences of metabolic type exhibited by different classes of organism are revealed, as we now know, in the first place by their different *nutritional* requirements. This recognition that the nutritional requirements of different micro-organisms, and indeed of different multicellular organisms, might be very different one from another, while nevertheless all these organisms used very similar *metabolic processes* for the building of their cell substance, was one outcome of a considerable period of study during which the immediate objective was to determine the exact nutritional requirements of many different species and strains of micro-organisms, mainly bacteria. This period of study overlapped with analogous studies on the vitamin requirements of higher animals; and initially studies of yeast nutrition were also conducted independently (12, 14). In order to understand the conception of essential metabolite correctly, it is worthwhile retracing the steps in nutritional studies which led to the recognition that nutritional requirements really reflect the relative abilities of particular species or strains of organisms to synthesize substances (metabolites) which are used commonly by the widest range of organisms. Then it will be possible to see to what extent and in what sense the expression essential metabolite has its validity.

Nutritional studies with yeast have a long history, the possibility of cultivating those used in the fermentation industry in media of known composition having been envisaged at an early period. An important date is 1901, that of the paper by Wildiers (36), who showed that certain yeasts required, in addition to the recognised grosser constituents of the culture medium, a very small but essential quantity of other material not at that time chemically defined. This paper thus emphasised the cardinal importance of certain "trace" substances among the essential nutrient requirements of at least certain yeasts. Studies of the exact nutrition of yeasts continued as an independent study for many years. In 1928, Eastcott (6) showed that *D*-inositol was an essential "trace" nutrient for a certain yeast, thus identifying the first of a group of nutrilites which many yeasts have since been shown to require. This finding was one of the earliest in which a special carbon compound of defined composition was shown to be a nutrient essential for a micro-organism, required in addition to the gross components (nitrogen source, glucose, salts) of the culture medium.

With bacteria, studies on the exact nutritional requirements of particular species were prompted by practical considerations very similar to those which initiated vitamin studies with higher animals, namely the observation of dietary exactingness. Thus some bacterial species were found to require special addenda to culture media which were ordinarily adequate for numerous other bacterial species. The examples of Johne's bacillus and *Haemophilus influenzae* were outstanding in drawing attention at a comparatively early date to the special nutrient requirements of some bacterial species. The heat lability of the *Haemophilus* V factor, subsequently found to be the diphosphopyridine nucleotide co-enzyme, cozymase (22), early drew attention to the existence of this growth-factor. The use of other acid-fast bacteria such as *Mycobacterium tuberculosis* or *Mycobact. phlei*, (the timothy-grass bacillus) as source of a growth-factor required by the difficultly cultivatable Johne's bacillus (*Mycobact. para-tuberculosis*), as found in 1912-13 by Twort & Ingram (32), likewise drew attention to another specific nutrient essential. In the 1930's a concentration of work began in order to make a more determined attack on the problem of the exact nutritional requirements of, in particular, bacteria of medical interest.

Many apparently separate lines of investigation on the exact nutritional requirements of various different micro- and other organisms came to a focus when pure thiamin at last became available. Then, in the course of a few years, between 1934-37, it was shown that this substance, first isolated as a vitamin essential in the nutrition of certain higher animals, (e.g. pigeon, man) was in fact also the substance which had been independently sought as a growth-factor for certain micro-organisms. Williams & Roehm (37) showed that thiamin had a marked growth stimulatory effect on certain yeasts; Schopfer (26) found that thiamin was the growth-factor he had sought for the fungus *Phycomyces blakesleeana*; Tatum, Wood & Peterson (30) found thiamin to be a growth-factor required by certain propionic acid bacteria; Knight (13) found that thiamin, or an equimolar mixture of its component pyrimidine and thiazole moieties, was essential for the growth of *Staph. aureus*; a similar observation was made for certain protozoa by Lwoff and Dusi (20) and Lwoff and Lwoff (21).

Thus what had been thought at first to be a number of different specific growth-factors were found to be one and the same substance, namely thiamin. This substance was therefore an essential nutrient for a number of organisms which differed widely in other biological respects. This fusion of several apparently different fields of work put them in an entirely new perspective, although the relationship between the nutrient requirements of the widely different organisms concerned—ranging from higher animals to certain protozoa, bacteria, yeasts and a fungus—appeared at first to be fortuitous.

As is now well known, subsequent studies on the exact nutrient requirements of micro-organisms have fused with animal vitamin studies in leading to the recognition of a number of substances which are required as nutrients for numerous other organisms besides those for which they were first detected as essential nutrients. That is to say, these substances are of *general* nutritional significance.

The growth-factors or essential nutrients which have been defined for one or



more species of micro-organism include all the vitamins of the B group, using the terminology of animal nutrition, and the majority of the naturally-occurring amino-acids. Some of the B group substances were in fact first detected through studies with micro-organisms and only subsequently implicated in animal nutrition. Among the B group of vitamins which have been discovered or subsequently recognised as essential nutrients of one or more species of micro-organism are: thiamin, riboflavin, nicotinic acid, pyridoxin, pantothenic acid, biotin and folic acid. Table I illustrates some of these points.

TABLE I  
*Common Metabolite Requirements of Different Organisms*

	FIRST RECOGNIZED AS ESSENTIAL NUTRIENT FOR:	SUBSEQUENTLY IMPLICATED IN NUTRITION OF:	ENZYME SYSTEMS:
Haematin.....	<i>Haemophilus</i> spp.	<i>Haemophilus</i> spp; pro- tozoa	Cytochromes, cata- lase, peroxidase
Thiamin.....	Higher animals	Bacteria, yeast, fungi, protozoa, plant roots	Thiaminoprotein en- zymes (e.g., pyru- vate decarboxyla- tion)
Riboflavin.....	Higher animals	Bacteria, fungi, insects	Flavoproteins
Nicotinic acid.....	<i>Staph. aureus</i>	Bacteria, yeasts, in- sects, plant roots, animals	Dehydrogenases
Pyridoxin.....	Higher animals	Bacteria, yeasts, fungi insects, plant roots	Amino acid decarbox- ylase, transamin- ase, tryptophanase (degradation and synthesis)
Pantothenic acid.....	Yeast	Bacteria, insects, ani- mals	Acetylation
Biotin.....	Yeast	Bacteria, fungi, insects, animals	? CO <sub>2</sub> fixation
Folic acid.....	<i>Strep. faecalis</i>	Bacteria, ciliate ( <i>T.</i> <i>gelii</i> ), insects, ani- mals	?

To this stage the substances under discussion have been considered only as essential nutrients required by one or more species of micro- or other organism. An important change of emphasis and of orientation occurred when it became evident that, in general, these substances—the vitamins of the B group and the amino-acids—were in fact synthesized by those organisms which did not require to be given them as nutrients. That is to say, all the organisms examined contained these substances of the vitamin B group. Different species, and, as subsequently became known, different strains within species, differed only in their abilities to synthesize the same group of substances which all required in order to be able to grow. One of these substances would thus become evident as an essential *nutrient* only when a given organism could not synthesize the compound for itself.

Once it had been recognized that substances which one species (or strain) of organism required as nutrients were in fact synthesized by other nutritionally simpler species, a more general conception became possible. It could then be suggested that the substances known as growth-factors were in fact needed for the growth of both synthesizers and non-synthesizers of the particular compounds. This implied that these growth-factors were essential ingredients of all living cells in which they were found, whether they were synthesized endogenously or not. In the latter case the cells acquired the essential substances preformed from the environment, as nutrients. Thus a nutritional requirement reflected an inability to synthesize a universally required substance. It was in order to emphasize this general *metabolic* function of many of the substances which had been initially discovered as *nutritional* essentials for specific organisms that Fildes (9) suggested the use of the term "essential metabolite," meaning thereby the substances involved "at each stage in any synthesis necessary for growth and without which, either synthesized or supplied from outside the cell, growth cannot occur." An essential growth-factor or nutrient is thus simply an essential metabolite or part of one, which a given species or strain of organism cannot synthesize.

This picture of the essential metabolic role of numerous substances which were first observed to have a biological role as nutrient essentials for particular organisms, is emphasized by a consideration of what these essential metabolic roles may be. There was no difficulty in regarding specific amino-acids as essential metabolites in the sense used by Fildes, since they are building blocks for protein which is generally accepted as an essential and characteristic component of all living matter. But it was not at first easy to see why the microbial growth factors of the vitamin B group were so universally distributed, since their metabolic functions were not at first known.

The first suggestion as to the function of a microbial growth-factor came when riboflavin was shown to be a component of Warburg's yellow respiration enzyme. Since then a function in one or more enzyme systems has been found or suspected for each of the microbial growth-factors belonging to the B group of vitamins, namely: thiamin, riboflavin, pyridoxin, biotin, pantothenic acid, folic acid and nicotinic acid. Thus thiamin pyrophosphate is the co-enzyme of pyruvate decarboxylase. Riboflavin, as riboflavin phosphate or flavin adenine dinucleotide, functions in various flavoprotein enzyme systems concerned, e.g., with the oxidation of the pyridine nucleotide co-enzymes (co-*zymase*, etc.), D-amino-acid oxidase, and the oxidation of hypoxanthine and certain aldehydes. Nicotinic acid is part of the di- and tri-phosphopyridine nucleotide molecules which are co-enzymes of various dehydrogenase systems (see 10a). Pyridoxin forms part of various enzyme systems concerned with amino-acid decarboxylation (2, 11); with transamination (33); with tryptophan synthesis from serine and indole (34); and with tryptophan breakdown (38). Pantothenate functions in certain acetylating enzyme systems (18, 19). Biotin is apparently implicated, it is not yet clear how directly, in carbon-dioxide fixation by heterotrophic cells (cf. 16, 28).

From the observations that these compounds of the vitamin B group, which might be called co-enzyme growth-factors when their nutritional role is in question, are generally found to be present in cells which do not need to be given them as nutrients and which must therefore have synthesized them, it may be concluded that the metabolic functions which these substances perform are essential for the life and multiplication of all the cells in which they occur. These thus appear to be vital and universally used metabolic processes for all cells growing under natural conditions.

It follows that interference with the carrying out of these essential metabolic processes would impair growth and perhaps kill the cells concerned. While this conception, stated generally, is to be found in the earliest developments of chemotherapy in Ehrlich's classical work, it was not really possible to give it a concrete interpretation until the advances of modern biochemistry had shown what these vital metabolic processes were. Ehrlich's brilliant and fundamental principle of interference with metabolic processes as a point of attack for chemotherapeutic agents remains. The advances of cell chemistry since Ehrlich's time have enabled the target to be much more specifically defined. Yet it is curious that the recognition that this was so had to await the relatively empirical discovery of the antibacterial action of the complex dyestuff prontosil. It was then soon shown by the French workers J. and Mme J. Tréfouël, Nitti and Boyet (31), with E. Fourneau in a later paper (10), that the important portion of the prontosil molecule was its sulfanilamide moiety, this latter substance being the effective antibacterial agent.

The next important step, and the one which linked the antibacterial effectiveness of the sulfanilyl group of chemotherapeutic drugs with a possible anti-metabolic effect, was the discovery by D. D. Woods (39) of the very specific action of *p*-aminobenzoic acid in annulling the antibacterial effect of sulfanilamide. Woods obtained, in crude form from yeast, material which prevented the antibacterial action of sulfanilamide and sulfapyridine, the quantitative relation of the bacteriostatic substances to the annulling yeast material resembling the competitive inhibition of an enzyme reaction by a substance structurally related to substrate or product. This, together with the chemical properties of the yeast material, suggested testing *p*-aminobenzoic acid, which was then found to be highly efficient in annulling the bacteriostatic effect of the sulfanilyl compounds. Woods showed that the *p*-aminobenzoic acid was highly specific; the *o*-compound was quite inactive and the *m*-compound had only 1 millionth of the activity of the *p*-isomer. The general conceptions about bacterial nutrition and essential metabolic processes which formed the theoretical background of the work of the (British) Medical Research Council's unit for research in bacterial chemistry, which has been described earlier in this article, made it reasonable to suppose that the action of a growth inhibitor might be due to its interference with an essential metabolic process. And it was with this theoretical background that Woods predicted that *p*-aminobenzoic acid itself was really an essential metabolite, and that it was with the proper functioning of this substance that the sulfanilyl compounds interfered.

Wood's prediction was soon verified when it was shown by Rubbo & Gillespie (25) that *p*-aminobenzoic acid was indeed a nutrient essential for *C. acetobutylicum*; later it was shown that other micro-organisms, e.g. *Acetobacter suboxydans* (15) and certain strains of *C. diphtheriae* (3) also required the substance as a nutrient essential. Subsequently, of course, it has been found that *p*-aminobenzoic acid is part of the pteroylglutamic acid (folic acid) molecule. Thus at least one function of *p*-aminobenzoic acid is known, namely as a building block for the synthesis of pteroylglutamic acid, itself a nutrient essential for certain micro-organisms and synthesized by many others.

This discovery of an essential metabolite, namely, *p*-aminobenzoic acid, by virtue of its annulling effect on a growth inhibitory substance, was the first example of its kind. All other growth factors had been first detected by reason of a dietary deficiency. It may well be that in the future other essential metabolites may be revealed in a way analogous to the discovery of *p*-aminobenzoic acid. Some growth inhibitors may be found whose inhibitory effect may be annulled rather specifically by suitable cell extracts, and by purification and identification of the active annulling material it may be possible to identify a new essential metabolite. This may afford one line of approach to finding the mode of action of some naturally-occurring antibiotics.

Fildes (9) put forward the conception, derived in large measure from the *p*-aminobenzoic acid-sulfanilamide relationship, that it might be possible to interfere with essential metabolic processes by means of suitable inhibitors modelled on the structures of the corresponding essential metabolites whose functioning it was desired to inhibit. Thus just as the bacteriostatic sulfanilamide is derived from the essential metabolite *p*-aminobenzoic acid by the substitution of a sulfonamide group for the carboxyl group of the metabolite, it should be possible to obtain other growth inhibitors by suitable structural alterations of the other known essential metabolites.

This generalisation put forward by Fildes for "a rational approach to chemotherapy" catalysed a very large amount of investigation along these lines, and hundreds of structural analogs of the known essential metabolites have been prepared. Many of these structural analogs have been found to have greater or lesser inhibitory action *in vitro*, specifically annulled by the corresponding essential metabolites upon which the analog has been modelled. It is true that no compound modelled on an essential metabolite other than *p*-aminobenzoic acid has yet been made which is as useful therapeutically as the bacteriostatic substances of the sulfanilyl group. But the importance of this conception of interfering with essential metabolic processes by means of inhibitors modelled on the structures of essential metabolites would appear to be valuable, because it does draw attention in a very concrete biochemical way to at least one kind of target in living cells at which a chemotherapeutic agent may be directed. And even if the design of a molecule suitable for interfering specifically with a given essential metabolic reaction is only the very first stage in constructing a successful therapeutic agent, it seems unequivocal that the information which may be acquired about the details of cell metabolism through



the use of structural analogs of essential metabolites will at the very least enlarge our understanding of cell-growth mechanisms. This in itself may be a prelude to the design of better and more specific chemotherapeutic agents.

To illustrate some of these possibilities a few examples of the activities of some structural analogs of essential metabolites may be considered. A few of the ways in which essential metabolite structures have been altered so as to produce inhibitory analogs may first be indicated; for a comprehensive view of this subject the reviews by Woolley (43) and by Roblin (23) should be consulted. The substitution of a *sulfonamide* for a carboxyl group has already been mentioned in the case of sulfanilamide *versus* *p*-aminobenzoic acid. The other compounds of the sulfanilyl group are in effect derived from sulfanilamide by the introduction of other groupings into the sulfonamide group; thus sulfapyridine has a pyridine ring so attached. Other metabolite analogs have similarly been obtained by substitution of a sulfonic acid or a sulfonamide group for a carboxyl group in other metabolites. Thus pantooyltaurine (thiopanic acid) is the sulfonic acid analog of pantothenic acid, against which it shows competitive inhibitions; a number of L-aminosulfonic acids, analogs of certain L-amino-carboxylic acids (amino-acids), showed inhibitory effects annulled by the carboxylic acids under appropriate conditions. The growth-promoting effect of pyridine-3-carboxylic acid (nicotinic acid) is likewise inhibited by the corresponding pyridine-3-sulfonic acid.

Another general method for producing inhibitory analogs of essential metabolites has been to change one or more atoms in a ring or chain. Thus the following pairs of metabolites and corresponding anti-metabolites may be cited: i) methionine and methoxinine (24); ii) phenylalanine and  $\beta$ -2-thienylalanine (35); iii) thiamin and pyritiamin (41, 42); iv) biotin and  $\gamma$ -(2,3-ureylene-cyclohexyl)-valeric acid (8), (fig. 1).

It is unnecessary to give further examples of the kinds of structural change which have been found to change essential metabolites into growth inhibitory analogs. In summary it may be said that inhibitory analogs have been prepared by relatively small modifications of the structures of all known essential metabolites; the change in structure must be sufficiently small so that a good deal of the original structure remains, yet sufficiently great so that the inhibitory analog can compete in some way with the functional use of the normal metabolite.

While there may be various ways in which inhibitors may interfere with the functional use of a normal essential metabolite, one of the most interesting and perhaps most specific modes of action would appear to be through competition for an enzyme associated with the normal usage of the essential metabolite, for example with enzymes concerned with the biosynthesis of the metabolite, or with enzyme systems of which the metabolite itself forms a functioning part.

To this point the main consideration has been with modifications of the structures of essential metabolites to make growth inhibitory analogs, and the biological background which makes this possible. But the biological situation

when an organism is presented with a structural analog of one of its essential metabolites is really a rather plastic one. The reaction of any given organism

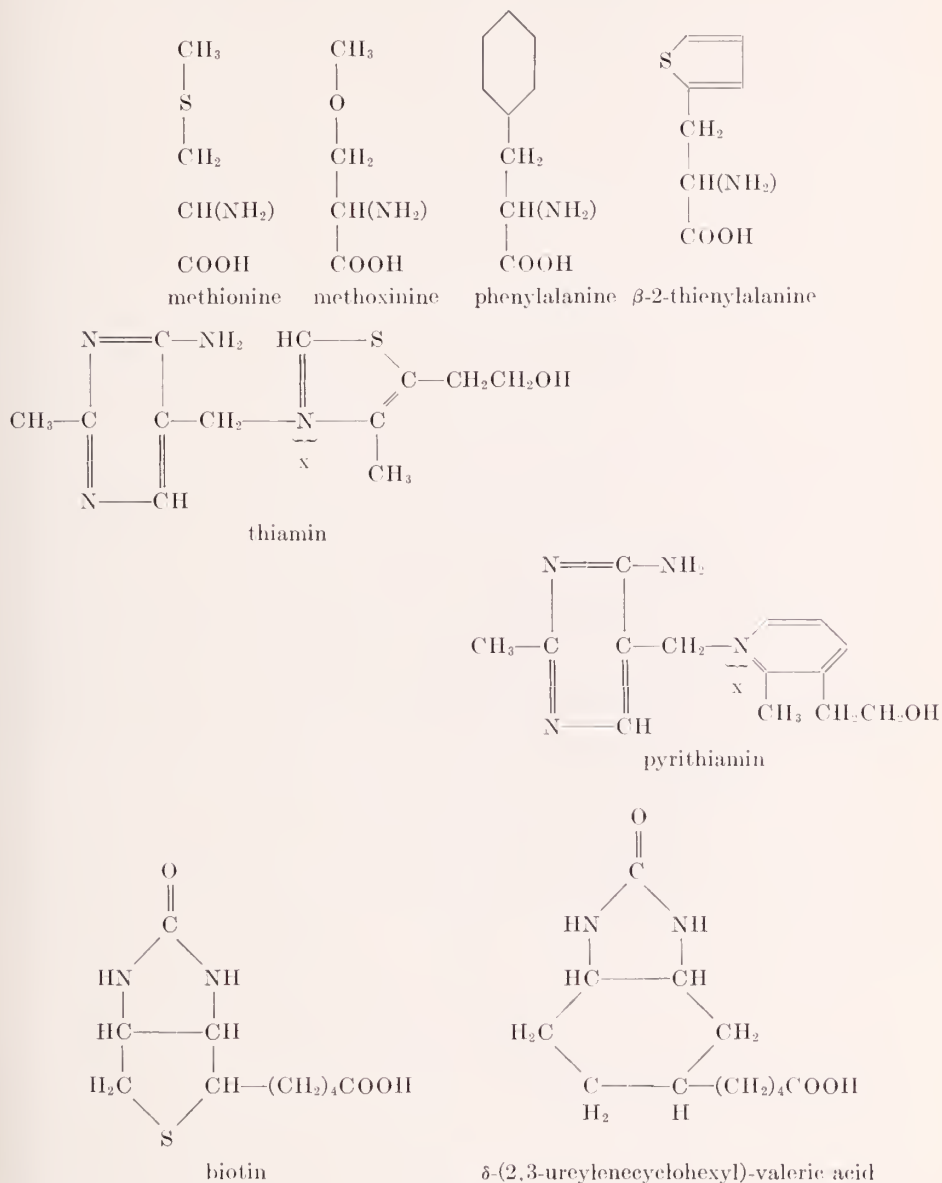


FIG. 1

to the structural analog must be considered dynamically; that is to say, the biochemical potentialities of the organisms themselves must be taken into account. Different species may react in different ways to the same metabolite

analog. Thus, the compound desthiobiotin is used as nutrient by *Saccharomyces cerevisiae* because it can make biotin from it (5). But with *Lactobacillus casei*, which cannot synthesize biotin and must be given it as an essential nutrient, desthiobiotin acts as a competitive inhibitor of biotin usage (4).

Gradations of activity from full vitamin activity to strong inhibitory effects may sometimes be observed when a series of related metabolite analogs are examined for their effects on different organisms. The effect in the case of any one compound and any one species or strain will be related both to the given structure and to the biological abilities of the given organism. Thus in the series of thiamin analogs in which the methyl group attached to the pyrimidine ring is replaced, respectively, by an ethyl, a propyl or a butyl group, it has been found that the ethyl derivative had practically full vitamin B<sub>1</sub> activity for rats (29), the propyl derivative some activity in pigeons (27), while the butyl derivatives evinced signs of thiamin deficiency, presumably by competing with a physiological function of the normal vitamin, the methyl compound (7).

Different susceptibilities of different species to a given metabolite analog may be due to different causes.

1. In some cases a metabolite analog may be converted to the normal metabolite; e.g. desthiobiotin to biotin by *Sacch. cerevisiae* but not by *Lb. casei*. *Endomyces vernalis* requires the pyrimidine moiety of thiamin as an essential nutrient; it can synthesize the vitamin thiazole and join it to the pyrimidine moiety, forming the metabolically essential thiamin. This organism is, ordinarily, susceptible to inhibition by pyrithiamin, an antimetabolite analog of thiamin in which the usual thiazole ring is replaced by a pyridine ring. A resistant strain of *Endomyces vernalis* was developed by Woolley (40), the resistance being due, at least in part, to ability to split pyrithiamin, the organism then using the pyrimidine moiety for the synthesis of thiamin proper.

2. A functional use may be made of the analog itself. O-Heterobiotin is an analog of biotin in which the sulfur atom is replaced by an oxygen atom. For some organisms O-heterobiotin and biotin have the same biological effect, growth promotion, e.g. in *Lb. arabinosus* Luckey (19) and there is evidence that the O-heterobiotin is used functionally as such (1). There is an analogous case in the use of certain substituted thiazoles which are apparently used functionally by pea-root cells instead of the normally required thiazole moiety of thiamin.

3. A metabolite analog which is to have an antimetabolite effect must not be destroyed too easily by the organism to be affected. Hence the effectiveness of substituting an "unphysiological" group such as a sulfonic acid or sulfonamide group for a normal group—e.g. a carboxyl group—in an essential metabolite, will depend on the inability of the organism to remove the abnormal group and thus render the antimetabolite no longer an effective competitor with the normal metabolite.

In summarising it may be said that the discovery of essential growth-factors has been one of the ways in which knowledge has been gained about the chemical

components of some universally used metabolic processes. Something is known about these apparently essential components of most forms of living matter. In growth, these compounds—among which may be mentioned the amino-acids and the co-enzyme group of growth-factors (the vitamin B group)—have to be acquired by all cells. This is done by more or less complete biosynthesis. The less complete the biosynthesis the more complex the material which has to be acquired exogenously, from the environment. To acquire these essential metabolites is vital to the life of the cells, and hence any interference with the acquirement and utilization of these compounds may impair life.

One way of interfering with the normal functioning of these vital metabolic processes is by the inhibition of the enzyme reactions by which these essential metabolites are synthesized or in which they are used. Competitive inhibition of the enzyme systems concerned with the biosynthesis or function of essential metabolites may be a potent method for interfering with these vital metabolic processes and for studying them.

Structural analogs of essential metabolites can enable the metabolism of growth to be modified and so studied. In some cases potent growth inhibitors may be found, although it is rarely possible, as yet, to predict whether a given structural analog will be inhibitory or not. Not enough is yet known about the biological and biochemical flexibility of the various organisms it might be desirable to inhibit. But it would seem that the conception that potent growth inhibitors of therapeutic value may be obtained by modelling structures on those of essential metabolites is a valuable one. At least this theoretical approach has the merit of emphasising and defining in a concrete way one kind of target in the organism to be attached, namely its essential metabolic processes. The study of growth-factors is one way of finding out what some of these essential metabolic processes are.

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## AMYOTROPHIC LATERAL SCLEROSIS<sup>1</sup>

### REPORT OF A CASE WITH INFLAMMATORY LESIONS AS A DOMINANT FEATURE

MORTON MARKS, M.D.

Amyotrophic lateral sclerosis, a disease form first so named and described by Charcot, is typified by a concomitant affliction of upper and lower neurons in the brain and spinal cord.

The early investigators of this disease considered it a manifestation of some form of abiotrophy, but subsequently a probable infectious origin came under discussion. More recently a deficiency state was given serious thought and this view was subjected to clinical tests.

There is still uncertainty under which of the foregoing etiologic categories the syndrome is to be classed. The selective involvement of both upper and lower motor neurons favors the concept of abiotrophy, a condition defined as a "premature loss of vitality or degeneration of certain cells or tissues not caused by any apparent external influence" (1). Such an interpretation, however, sheds little light on the actual causation of the disease; moreover, the infrequency of amyotrophic lateral sclerosis in families, the rare examples of direct inheritance, and the onset of symptoms relatively late in life speak against abiotrophy as the dominant causative factor. Moreover, the selection of certain systems in the cord and brain is not limited in its occurrence to degenerative diseases, as inflammatory processes also may have selective points of attack; in poliomyelitis, for example, the virus attacks the ventral gray substance.

On the other hand, in 1938 Einarson and Ringsted (2) described degenerative changes in the anterior horn cells, pyramidal tracts and posterior columns in rats deprived of Vitamin E. They suggested the possibility that in amyotrophic lateral sclerosis in man, a deficiency of this vitamin might be the cause. When synthetic  $\alpha$ -tocopherol became available, a number of cases of amyotrophic lateral sclerosis were subjected to intensive Vitamin E therapy, and promising results were reported by Bicknell (3) and Wechsler (4, 5). Encouraged by these early reports, more extensive studies were undertaken, but the results, unfortunately, were not as gratifying as had been expected. Experimental studies by Wechsler and Globus (6) on monkeys deprived of Vitamin E failed to produce clinical evidence of involvement of the nervous system. Histo-pathological changes comparable to those produced in lower animals were not found. Because deprivation of Vitamin E failed to reproduce the syndrome experimentally in higher animals and because patients responded poorly to its administration, Vitamin E deficiency has been abandoned as a significant factor in the pathogenesis of amyotrophic lateral sclerosis.

The possibility of infection as the cause of amyotrophic lateral sclerosis has been extensively investigated. Attempts to isolate bacteria or viruses from cerebro-spinal fluid or from autopsy material were uniformly unsuccessful, and

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efforts to transmit the disease have failed (7). Despite these failures, many investigators nevertheless felt that this disease was probably infectious. Cases occurring in the wake of epidemic encephalitis were described. Wimmer (8, 10) and Wimmer and Neel (9) presented five cases of amyotrophic lateral sclerosis following chronic encephalitis. In three of these cases autopsy studies disclosed histologic evidences of inflammation. Among these, slight perivascular lymphocytic infiltrations were scattered throughout the medulla and spinal cord. Wimmer concluded that the syndrome of amyotrophic lateral sclerosis can be produced by the etiologic agents of syphilis or epidemic encephalitis. He tempered this, however, by the observation that "to conclude an exogenous origin of all cases would be imprudent because of the small number of cases studied."

Other cases occurring as a sequel to epidemic encephalitis were described by Gilpin (11), Guillaín and Alajouanine (12), Jansco (13), Ornsteen (14), Deconrt, Mathieu and Meyer (15) and Bau Prussak (16).

It is now generally agreed that syphilis does not play a significant role in the pathogenesis of amyotrophic lateral sclerosis (17, 18), but it has been pointed out that a syphilitic myopathy (19, 20, 21) might be confused with progressive muscular atrophy or amyotrophic lateral sclerosis (22). In these cases, however, the amyotrophy precedes the signs of spasticity and the evolution of the condition is much slower. Serologic studies are important in the differential diagnosis. In a series of 81 cases reviewed by Kaiser (23) 79 per cent had a positive blood Wassermann; 69.5 per cent had a positive spinal fluid Wassermann. The albumin and globulin content of the cerebrospinal fluid was increased in all cases.

Although the French and German literature contains numerous references to cases of amyotrophic lateral sclerosis in which there are indications of an inflammatory pathogenesis, this factor has received little attention in the American literature. A case, therefore, in which the pathological findings are predominantly inflammatory is described.

*History* (Adm. #475237, P.M. #12085). A tailor, aged 51 years, was admitted to the Mt. Sinai Hospital with a history of increasing weakness of the hands, to a lesser extent on the left, of three months duration. In addition, there were "twitchings" in both shoulder regions and in the lower part of the neck. There had been some hoarse ness for two to three months, and a weight loss of six pounds during this period.

*Neurological examination.* Corneal reflexes were sluggish bilaterally. There was a tremor of the tongue but no atrophy or fibrillations; the other cranial nerves were normal. There was generalized muscular weakness, most marked in the upper extremities, the right more than the left. There was weakness of the right hand, and of flexion and extension at the wrist. Both deltoid and pectoralis muscles were atrophied, more marked on the right side. The right forearm and right thenar eminence showed a questionable atrophy. Fibrillations were seen in both upper extremities, including the deltoid region, and were most marked on the right. Motor power in the lower extremities was fair. There was a questionable slight diminution on the right, but no atrophy or fibrillations were noted. The deep reflexes were generally depressed except for the left biceps, both triceps, and the right patellar, which were normal. Abdominal reflexes were slightly diminished bilaterally; the cremasteries were active and equal. There were no pathological reflexes. Sensation was normal.

*Laboratory and other observations.* Urine and blood count were normal. Blood serology

was negative. Blood urea nitrogen, 18 mg. per cent; blood uric acid, 7 mg. per cent; blood sugar, 85 mg. per cent; blood cholesterol, 270 mg. per cent. Lumbar puncture: Initial pressure, 130 mm. of water; fluid, crystal clear and colorless; 3 lymphocytes per cubic mm.; Pandy, 1 plus; colloidal gold curve, negative; Wassermann negative; globulin negative; total protein 46 mg. per cent. X-ray of the cervical spine showed fairly marked osteoarthritic changes, particularly involving C2, C5, C6, and C7. X-ray of the chest showed what appeared to be several small areas of focal atelectasis with some pleural thickening. Electrocardiogram showed no abnormality other than a left axis deviation. The heart was enlarged to the left. Blood pressure, 147 systolic and 100 diastolic.

*Course.* A diagnosis of amyotrophic lateral sclerosis was made. The patient was given intensive vitamin E therapy and discharged with a daily maintenance dose. When seen in the follow-up clinic one month later, the fibrillations previously noted were still present and there was no evidence of improvement. He complained of breathlessness after slight

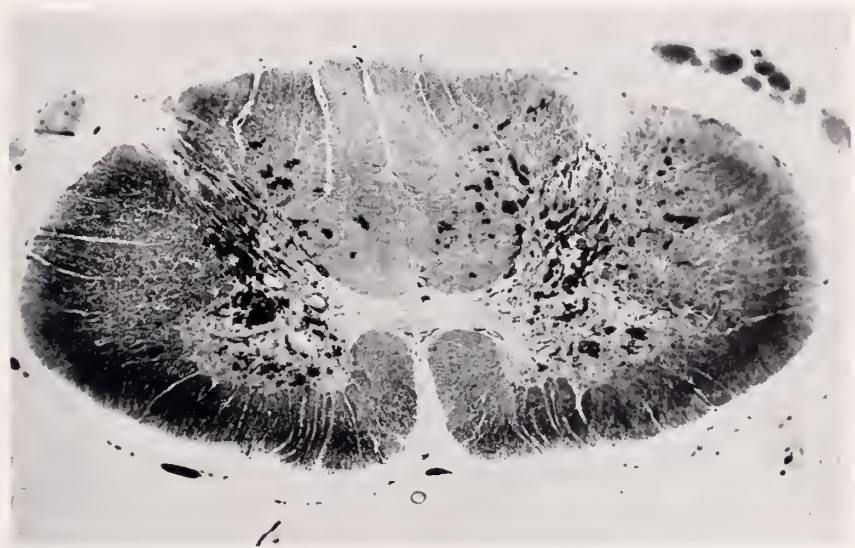


FIG. 1. Section of the spinal cord, cervical region, showing demyelination affecting the lateral and ventral pyramidal tracts and posterior columns, with many small areas of hemorrhage in the gray matter. Photomicrograph, Weil myelin stain.

exertion. Fluoroscopy showed movement of both diaphragms and a consultant ascribed the dyspnea to a reduction of strength of the muscles controlling the thoracic cage. Vitamin E was continued and he again returned to the clinic three months later reaffirming his previous complaint of marked dyspnea on slight exertion and continued weakness of the upper extremities. Examination showed that he was using the accessory muscles of respiration in breathing. The fibrillations in both upper extremities were marked. Six weeks later he was re-hospitalized because of increasing respiratory difficulty.

*Second admission: Examination.* Showed a large, smooth, beefy tongue, a slightly emphysematous chest, blood pressure of 146 systolic and 90 diastolic, and a protruding abdominal wall. There were weakness and atrophy of the muscles of the upper extremities and fibrillations were marked. There was some atrophy and weakness of the lower extremities. Deep reflexes were hypoactive, except for the triceps. Abdominal reflexes were present. There were no pathological reflexes. Sensory examinations were normal.

*Laboratory data.* Urine, normal. Blood studies: hemoglobin, 81 per cent; white blood cells, 5,600 per cubic mm., Wassermann, negative; sugar, 80 mg. per cent; urea nitrogen,



15 mg. per cent; blood vitamin E, 0.5 mg. per cent and 0.63 mg. per cent. On a regular diet there was 50 mg. of creatine in a twenty-four hour urine specimen. Circulation time

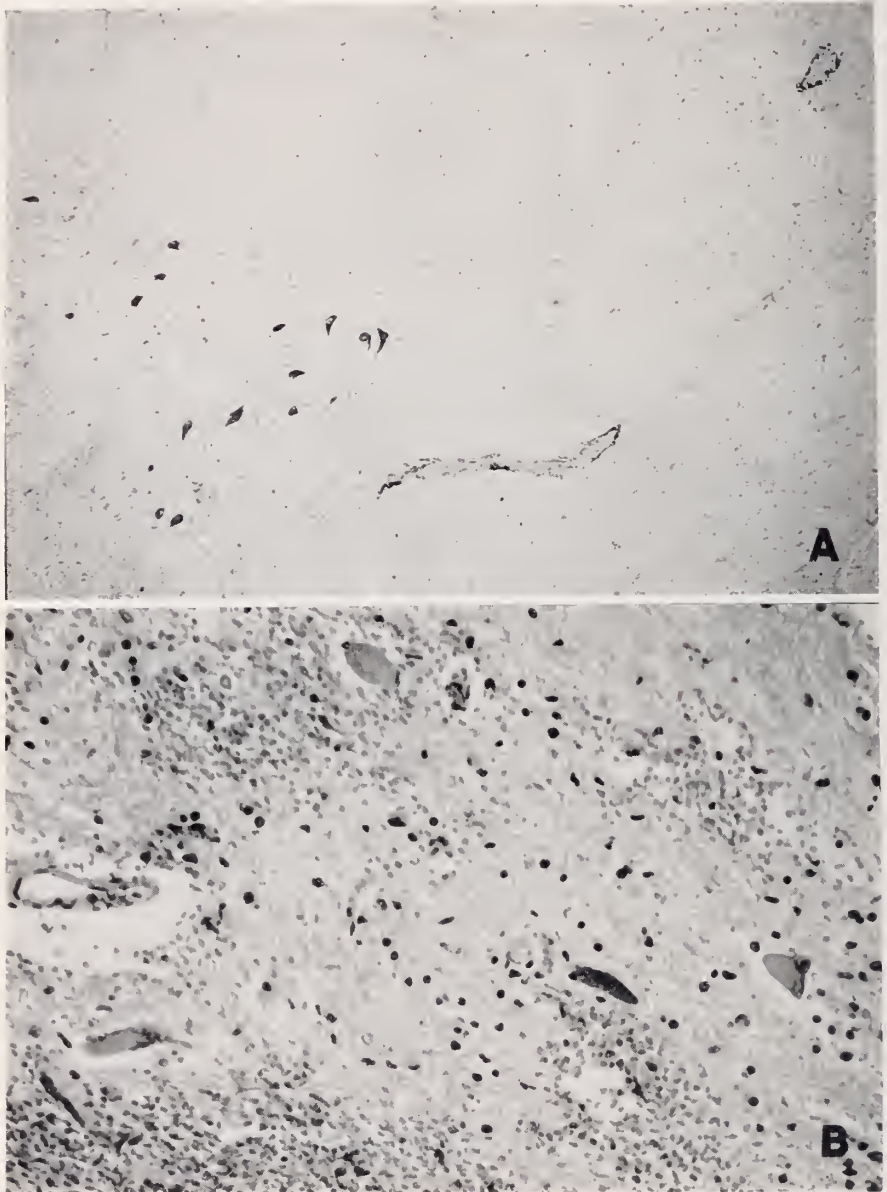


FIG. 2. A. Section of the spinal cord, cervical region, showing a great reduction in the number of cells of the anterior horns and perivascular infiltrations of neighboring blood vessels. Photomicrograph, hematoxylin and eosin stain,  $\times 53$ .

B. Section of the spinal cord, cervical region, showing advanced degenerative changes of the anterior horn cells and a number of small hemorrhages. Photomicrograph, hematoxylin and eosin stain,  $\times 250$ .

(calcium gluconate) was 12 seconds. X-ray examination of the chest showed horizontal linear streaks of focal atelectasis at the right base.

*Course.* He continued to be dyspneic and orthopneic. A slowly developing generalized hyperkeratotic folliculitis was noted, diagnosed by the consultant dermatologist as due to vitamin A and B deficiency, for which he was treated with yeast and viosterol. In

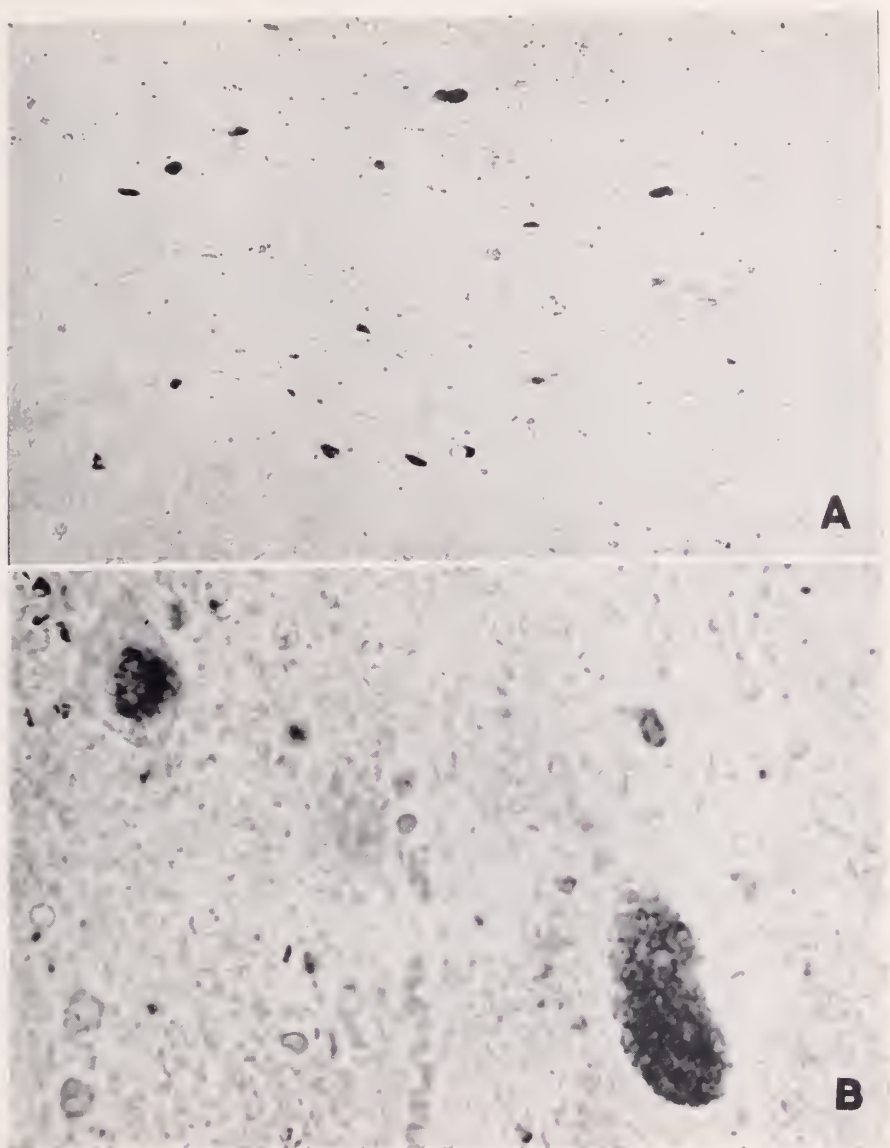


FIG. 3. A. Section of spinal cord, cervical region, showing anterior horn cells crowded with fat particles. Photomicrograph, scarlet red stain,  $\times 90$ .

B. Same section, under higher magnification, showing fat laden cells,  $\times 610$ .

addition to oral vitamin E daily intramuscular administration of  $\alpha$ -tocopherol was again begun on the twenty-fourth day in the hospital. On the twenty-sixth day he developed increased respiratory difficulty and became cyanotic. Nasal oxygen was administered but the patient expired a few hours later. Post-mortem examination was limited to the brain and spinal cord.

*Necropsy findings. Gross.* The brain and spinal cord were removed intact. The scalp, calvaria and dura were normal. There was a moderate diffuse injection of the vessels over the surface of the hemispheres. The sulci and gyri appeared normal. There were no areas of softening or discoloration. The dural sinuses were all patent. The pituitary gland was normal in size and shape.

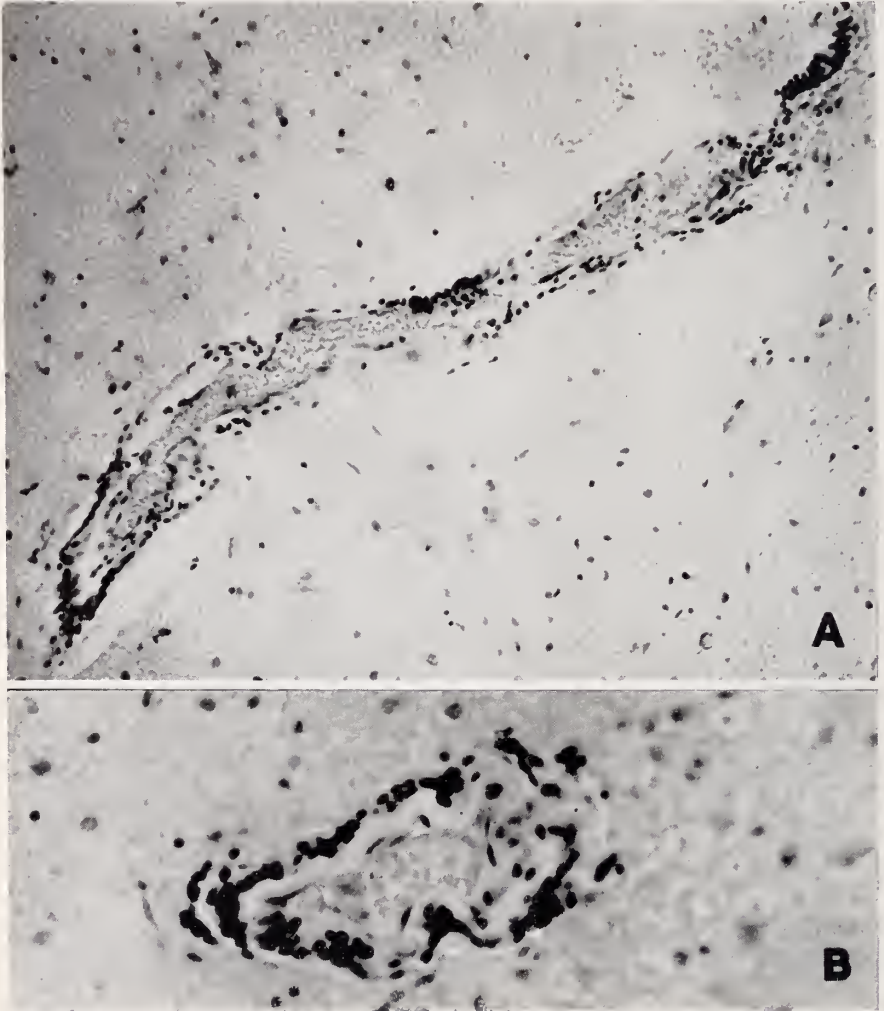


FIG. 4 (A and B). Section of the spinal cord, cervical region, exhibiting perivascular infiltrations (fig. 2A). A.  $\times 215$ ; B.  $\times 345$ .

The spinal cord showed no gross abnormality in external appearance. The brain and cord weighed 1620 grams.

On sectioning of the cord at the level of the cervical enlargement there was a marked congestion, appearing almost hemorrhagic, in the gray matter, particularly in the anterior horns. This was not present at the lumbar enlargement. The circumference of the cord showed no reduction in size at any level.

*Microscopic findings.* The spinal cord, (cervical, thoracic, and lumbar) segments and

the medulla oblongata at the level of the decussation revealed in myelin stain preparations mild diffuse degenerative changes throughout the white matter affecting principally the ventral and lateral pyramidal tracts and posterior columns. Most striking were the many small areas of hemorrhage dispersed throughout the gray matter of the cervical segments of the spinal cord (fig. 1).

In the same region there was a significant loss of cells in the anterior horns and a moderate degree of perivascular infiltration of the adjacent blood vessels (fig. 2a); many of the remaining anterior horn cells showed signs of degeneration, such as swelling, loss of normal outline, chromatolysis, eccentricity of nuclei, absence of nuclei and an increased amount of lipochrome pigmentation in the cytoplasm; some of the many small hemorrhages interspersed throughout the gray matter formed rings about the blood vessels (fig. 2b).

Sections of the cervical and lumbar cord stained by the Scharlach Red method showed many of the anterior horn cells to be packed with fat (fig. 3). This finding was more marked in the lumbar region. Bielschowsky preparations of the cervical and lumbar cord showed some tortuosity and thickening of the neurofibrillae of the anterior horn cells.

Sections of cerebral cortex stained by the Nissl method revealed fairly good preservation of the nerve cells.

*Comment.* This patient died ten months after the initial onset of symptoms and offered a problem in diagnosis, primarily because of the absence of pyramidal tract signs. From the clinical as well as the pathological findings this might be considered by some to be a case of subacute anterior poliomyelitis. However, neither subacute or chronic poliomyelitis has ever been proven to be a definite pathological entity. At the present time amyotrophic lateral sclerosis is considered by most investigators to be a combined upper and lower motor system disorder that may show all gradations of involvement of the two systems, ranging from a primary degeneration of the pyramidal tracts (the so-called "primary" lateral sclerosis) on the one hand, to a chronic degeneration of the anterior horn cells (in the nature of a chronic poliomyelitis) on the other. The classical variety, as originally described by Charcot, lies nosologically somewhere between these two (24).

In this case, the perivascular infiltrations were fairly well marked, scattered throughout the spinal cord, both in the gray and white substance and consisted predominantly of small round cells (fig. 4). They were seen in areas in which there was little or no evidence of degeneration.

#### DISCUSSION

Early observers, suspecting that this disease might sometimes be inflammatory, subjected cases to careful histologic investigation. Dreschfeld (25) reported a case in 1885, with a two year history of progressive weakness and atrophy of the right lower extremity with terminal involvement of the upper extremities, in which, in addition to the atrophic changes disclosed in the anterior horn cells, some periarterial cell infiltrations were found near the central canal and in the lateral columns. In the dorsal and cervical regions some sclerosis of the lateral columns was noted in addition to the perivascular infiltrations.

Mott (26), in 1894, reported a case in which the leptomeninges showed chronic inflammatory changes. Loesewitz (27) in his study of amyotrophic lateral sclerosis, reported in 1896, "many of the vessels show a significant increase of



nuclei in their walls, so that, thereby, the perivascular spaces are narrowed; in addition other cells lie in the perivascular spaces, consisting of a nucleus surrounded by a ring of protoplasm, which does not show granular elements by the usual method of fixation."

Bielschowsky (28) reported a case in which hemorrhages were found in the anterior horns extending from the lumbar to the upper cervical region, which he regarded as evidence of inflammation. There was some slight perivascular round cell infiltration and many newly formed blood vessels.

In a case observed by Pilez (29), enlarged perivascular lymph spaces infiltrated with round cells were found throughout the entire spinal cord.

Grunow (30) reported a case with cellular infiltrations about the arteries of the anterior fissure and about some of the vessels of the anterior horns and white matter. Necrotic foci were present in the crossed pyramidal tracts and there were small hemorrhages in the gray matter. The nerve cells of the anterior horns and the anterior and lateral columns showed degeneration.

In their study of the pathogenesis of amyotrophic lateral sclerosis, Czyhlarz and Marburg (31) noted some perivascular round cell infiltration in the spinal cord. They considered the process to be a primary degeneration, pointing out that the presence of the slight perivascular infiltrations is a finding not seen in secondary degeneration.

In a case studied by Phillips (32), the medulla revealed small areas of perarteritis with small cell infiltrations of the adjacent gray matter.

Haenel (33) reported round cell infiltrations in the adventitia of the small vessels throughout the entire central nervous system. Only the region of the posterior columns was relatively free of vessel changes.

Meyer's case (34) revealed adventitial infiltrations of plasma cells and lymphocytes throughout the spinal cord, most marked in the cervical region, but also present somewhat in the medulla, pons and cortex. This case, however, also showed multiple cysticerci in the brain, and the significance of inflammatory vessel changes was discounted by subsequent investigators.

Buscher (35) found only slight perivascular infiltrations which were confined almost exclusively to the nuclear regions.

Naito (36) reported changes in the nerve cells and fibers of the cortex and an increase in the number of glial elements. Isolated vessels showed infiltrations of plasma cells and small glia cells in the perivascular spaces. The changes in the spinal cord were similar to those found in the cortex, but more marked. He concluded that the entire process is inflammatory in nature because of the presence of the perivascular infiltrations similar to those found in cases of poliomyelitis.

Matzdorff (37) recorded three cases of amyotrophic lateral sclerosis with histologic findings he considered indicative of a primary inflammatory process. The leptomeninges were hypertrophied, adherent, and infiltrated with small round cells. Limited entirely to the white matter, there was an alterative, productive and slightly exudative process with the morphologic characteristics of an inflammation. The perivascular spaces were dilated and contained a number

of lymphocytes and plasma cells. He contended that the work of the earlier workers should be reviewed, since they were concerned primarily with the localization of the process and therefore they might easily have overlooked or failed to emphasize the inflammatory changes present. The author concluded that the pathogenesis of amyotrophic lateral sclerosis is of a toxic infectious nature in which the mode of infection is similar to that seen in tetanus.

Souques and Alajouanine (38) reported a case in which perivascular infiltrations were found in the gray matter of the cord and in the reticular substance of the medulla. They attempted experimentally to transmit this disease to guinea pigs and rabbits. One of two rabbits, inoculated intracerebrally with an emulsion of spinal cord taken from the patient, developed atrophy of the hind paws six months later. The nervous system disclosed lesions in the spinal cord comparable to those seen in the patient. These investigators considered significant the fact that the perivascular infiltrations, which were present in considerable degree in several places in the cortex, did not extend to the site of inoculation. They concluded that subacute anterior poliomyelitis is a specific infection caused by a filterable neurotropic virus with a long incubation period.

In another case reported by Alajouanine (39) a discrete adventitial reaction was found in the upper part of the cord. In the spinal pia there was an increased number of lymphocytes, and in the region of the posterior collateral septum there was a dense mass of lymphocytes mixed with a perivascular reaction.

Poussepp and Rives (7) reported three cases of amyotrophic lateral sclerosis which disclosed perivascular infiltrations scattered throughout both white and gray matter, extending from the cortex to the spinal cord. They considered amyotrophic lateral sclerosis to be an infection, despite their inability to produce positive proof for this hypothesis by the injection into rabbits of cerebrospinal fluid taken from their patients.

D'Antona and Tonietta (40) reported a case with perivascular infiltrations in the spinal cord and brain stem, present in both gray and white substance, primarily in the former, and most prominent in the cervical region.

Van Bogaert (41) reported a case showing lymphocytic perivascular infiltrations in the cervical cord, bulb and midbrain. In the meninges around the posterior roots of the thoracic region there was an infiltration composed almost exclusively of lymphoid cells and a few macrophages.

Nakamura (42) concluded from histologic studies of four cases of amyotrophic lateral sclerosis that the lesions were essentially inflammatory in nature with precisely the same localization as poliomyelitis but of a more chronic character. In two cases changes were also found in the cerebral cortex. Although the process was less marked than in true poliomyelitis, he felt that there was no doubt as to its inflammatory character. There was an exudate consisting of adventitial and lymphoid cells. The pyramidal tracts were degenerated in the anterior as well as in the lateral columns, and there were perivascular accumulations of compound granular cells.

A case reported by Wechsler and Davison (43) disclosed "perivascular infiltrations, consisting primarily of cells of glial origin" in the centrum ovale and in the

white matter of the temporal and parietal lobes. In the internal capsule there was an area of perivascular infiltration consisting of compound granular corpuscles and glia cells.

Schaffer (44) reported a case in which there were slight round nuclear collections present around the veins of the anterior fissure.

Ectors (45) reported finding a marked perivascular reaction, consisting mainly of histiocytes and lymphocytes, extending from the bulb to the lumbar region in case of three and a half months' duration. There was no demyelination present. He regarded the perivascular reaction as indicative of infection.

Margulis (46) studied three cases and noted thickening and adherence of the leptomeninges to the periphery of the cord, most severe in the lower portion. He found a slight perivascular infiltration present in the region of the degenerated pyramidal tracts in one of the cases. The perivascular spaces of the anterolateral columns were dilated and filled with a granular, amorphous mass which he believed was coagulated lymph. From the "lymphstasis" he concluded that the pathogenesis of amyotrophic lateral sclerosis is infectious-toxic, and the spread of the process is lymphatic, involving the antero-lateral portion of the spinal cord.

In a subsequent work, Margulis (47) studied six cases more intensively. Inflammatory changes were present in the dura. The leptomeninges, as well as the vessels of the anterior spinal fissure, were infiltrated with lymphocytes. At times the infiltrated vessels of the arachnoid spaces could be followed as they entered the cord. The epidural tissue was always inflamed, but this was not necessarily related to the presence of the inflammatory changes in the dura. In the intrameningeal portion of the spinal roots he found a peri- and endoneuritis, with a loss of root fibers. In the spinal ganglia, the vessels were infiltrated and there was a proliferation of connective tissue. The author suggested that amyotrophic lateral sclerosis is a diffuse disease of the entire nervous system with a lymphatic spread. He concluded that it is a symptom complex which may be caused by various agents; the epidural tissue forms the point of origin and primary fixation of the virus, from which it extends, through the clefts in the dura and along the perineural and perivascular spaces, into the subarachnoid space.

In contrast to these observations, Holmes (48) studied ten cases and only exceptionally was there a round cell infiltration of a mild degree found in the adventitial sheaths.

Similarly, Ottonello (49) studied five cases and concluded that the perivascular infiltrations occasionally found are so slight as to be considered secondary to the process of degeneration.

A lack of inflammatory phenomena has also been recorded by Hassin (50, 51), Pekelsky (52), Warner (53) and others.

Perivascular infiltrations are considered to be one of the earlier and fairly constant manifestations of inflammation. It must be borne in mind, however, that they can be found not only in inflammatory processes, but also in regions of severe tissue destruction, for example, in hemorrhage, encephalomalacia, and in zones surrounding tumors. Only from the nature of the associated pathological

findings can they be recognized as "secondary" or "symptomatic" (54, 55). Some have concluded that a comparable situation exists in amyotrophic lateral sclerosis, and that the perivascular infiltrations are secondary to the primary degeneration of the nerve elements (56). Matzdorff (37), on the other hand, considers them as indicative of a primary inflammation because of the severity of the findings, their presence in the vicinity of healthy nerve fibers, the finding of blood pigment and the inflammatory involvement of the meninges.

In the case herein reported, it was noted that the perivascular infiltrations were found in the spinal cord, not in association with areas of marked degeneration, and were therefore considered indicative of a primary inflammatory process.

Five additional cases of the amyotrophic lateral sclerosis were reexamined, with emphasis on the presence or absence of perivascular cell accumulations. In every case, scant, incompletely enveloping collections of small round cells were found dispersed throughout the entire central nervous system. In many of the cases these collections were seen only after prolonged search and examination of a number of sections. In order correctly to evaluate the significance of this finding, a study was made of the brains and spinal cords of patients of comparable ages who had come to autopsy without a history of neurological disorders or complications. In these cases similar scant perivascular accumulations were found distributed throughout the brain and spinal cord. The impression was obtained from this study that the perivascular phenomenon was slightly more marked in the cases of amyotrophic lateral sclerosis than in the controls. There was no exact method, however, whereby such a slight difference could be conclusively demonstrated.

#### SUMMARY

1. Amyotrophic lateral sclerosis is a disease syndrome the cause of which is still unknown. It is a combined upper and lower motor system disorder that may show all gradations of involvement ranging from "lateral sclerosis" to "chronic poliomyelitis."

2. The older concept of an abiotrophy and the more recent of a deficiency state as significant etiologic factors are discussed.

3. The role of infection and the relationship of this disease to epidemic encephalitis and syphilis are considered.

4. A case in which the histologic findings were predominantly inflammatory is described in detail. These consisted primarily of hemorrhages and perivascular infiltrations.

5. Five other cases of amyotrophic lateral sclerosis were examined for the presence of perivascular infiltrations. Although scant collections of small round cells were found, comparison with a control series of non-neurological cases failed to reveal significant differences.

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## SYSTOLIC CLICK

### VARIATION OF POSITION WITH APPEARANCE IN EARLY DIASTOLE CASE REPORT\*

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Systolic gallop, as first described by Cuffer and Barbillon (1) in 1887, included various sounds heard in systole. With the introduction of graphic registration of heart sounds, extra sounds in systole were more accurately differentiated. According to Wolferth and Margolies (2), they may be classified as reduplicated first sound, apical systolic gallop rhythm, aortic systolic gallop rhythm, semilunar opening click and mid-systolic click. The clinical importance of these sounds lies in the fact that occasionally they give rise to a cadence which may be mistaken for diastolic gallop rhythm. This differentiation is important, since extra sounds in systole have no prognostic significance, while diastolic gallop rhythm is usually associated with a poor prognosis.

We recently have had the opportunity to observe a patient with sarcoidosis in whom an extra sound in the cardiac cycle was discovered. It fell into the classification of a "mid-systolic click" in that it occurred between the first and second sounds, was clicklike and varied in its position within the cardiac cycle (2). At times it was recorded in early diastole. It is our purpose to demonstrate accurate graphic studies of this sound, to prove its extracardiac origin and, possibly, to shed some light on its cause.

#### CASE REPORT

H. W., a 40 year old white male, was admitted to The Mount Sinai Hospital (Service of Dr. George Baehr) in January, 1947, complaining of dyspnea; loss of weight; a dry, non-productive cough of 4 months' duration; and cyanosis of 5 weeks' duration.

The patient was a well-nourished, well-developed, cyanotic, dyspneic white male with a non-productive cough. The temperature was 98.6°F., pulse 76, respiration 20 and blood pressure 110 systolic and 65 diastolic. Positive physical findings were limited to the heart and lungs. Examination of the lungs revealed roughening of the inspiratory breath sounds throughout. The heart was not enlarged; the sounds were of good quality. The pulmonic second sound was louder than the aortic second sound. There was a soft apical systolic murmur. The liver was felt one fingerbreadth below the right costal margin.

The sedimentation rate was 40 mm./hour (Westergren). The venous pressure was 15.5 centimeters; pressure over the right upper quadrant produced no rise. The arm to lung circulation time was 7 seconds (ether) and the arm to tongue time was 10 seconds (saccharin). The vital capacity was 2100 cc. Roentgen examination of the chest showed bilateral interstitial infiltrations extending from the hilar regions to the periphery. The hilar nodes were enlarged. The heart size was within normal limits.

Boeck's Sarcoid was suspected. A skin test for sarcoidosis was positive. Lymph node biopsy performed at this time was not confirmatory. Nitrogen mustard therapy was instituted and marked improvement in the subjective symptoms resulted. There was no change, however, in the x-ray findings.

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FIG. 1. Roentgen film of chest showing diffuse interstitial infiltrations, hilar adenopathy and normal heart size.

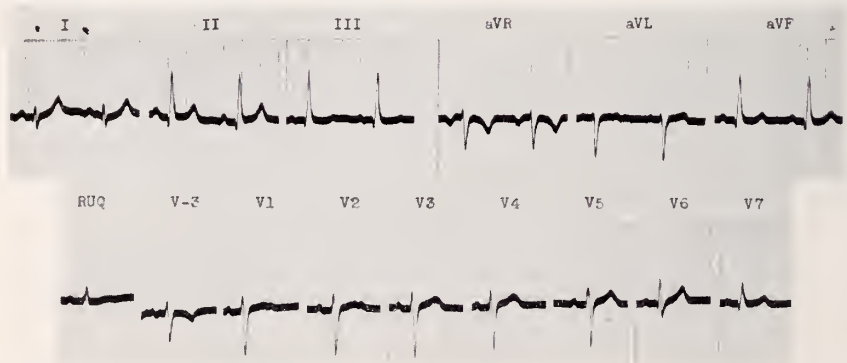


FIG. 2. Normal electrocardiogram with vertical electrical axis, clockwise rotation and upright QRS in the right upper quadrant lead. RUQ—right upper quadrant lead.

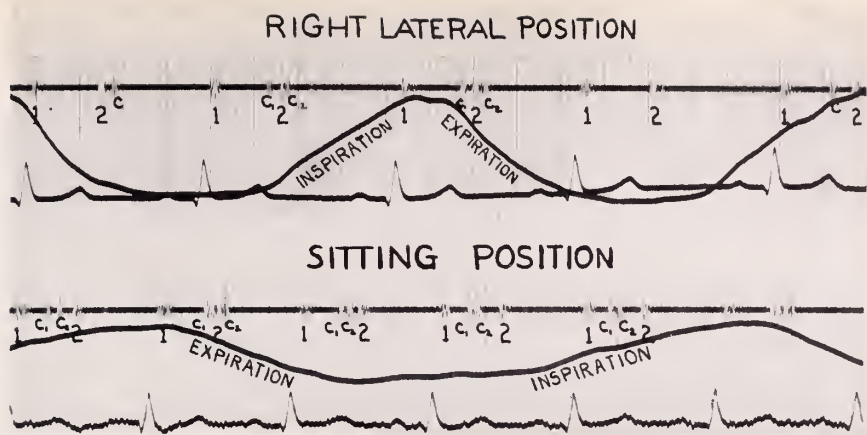


FIG. 3. The effect of respiration on the extra-cardiac click. 1—1st heart sound. 2—2nd heart sound. C—extra-cardiac click. C<sub>1</sub>—1st component of click. C<sub>2</sub>—2nd component of click.

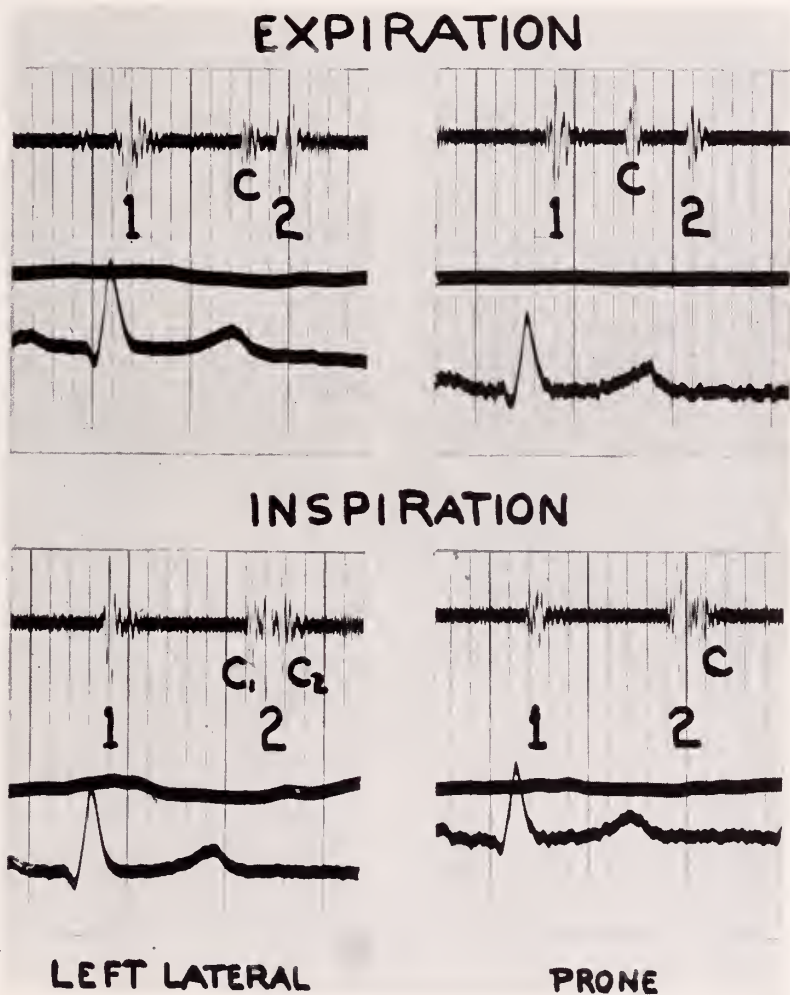


FIG. 4. The effect of body position and breath holding in deep inspiration and expiration on the extra-cardiac click. Note: On deep inspiration the click is recorded in diastole. 1—1st heart sound. 2—2nd heart sound. C—extra-cardiac click. C<sub>1</sub>—1st component of the click. C<sub>2</sub>—2nd component of the click.

The patient was readmitted one year later, complaining of recurrence of dyspnea. At this time a right epitrochlear node showed lesions characteristic of Boeck's sarcoid. Roentgen examination of the chest revealed no new changes (fig. 1). The physical examination was similar to that of the previous admission except for the heart sounds. The PMI was in the 5th interspace at the mid-clavicular line. The rhythm was regular. The rate was 92. The blood pressure was 130 systolic and 70 diastolic. The sounds were of good quality. The pulmonic second sound was louder than the aortic second sound. A short, click-like sound was clearly audible before the second sound. At times this was split into two components and its position in the cardiac cycle varied. It was heard over the entire precordium with maximal intensity parasternally at the left 5th interspace. The intensity varied with the patient's position but the extra sound never disappeared. It was diagnosed clinically as an adventitious sound probably of extra-cardiac origin. The cardiac contour was normal by fluoroscopy and teleroentgenogram. The routine electrocardiogram (fig. 2) was not abnormal. There was a tendency to right axis deviation in the standard leads. The augmented unipolar extremity leads demonstrated a vertical electrical position of the heart. In the unipolar precordial leads the transition pattern was shifted to the left. A lead from the right upper quadrant showed an upright QRS of 3.5 mm.

Phonocardiographic studies recorded the extra sound over the entire precordium with maximum amplitude at the left 5th interspace parasternally. The extra sound showed no constant relation to any phase of the cardiac cycle, as demonstrated by simultaneous tracings of the jugular pulse, carotid pulse and the electrocardiogram.

It was found, however, that a definite and predictable relationship existed between the sound and the respiratory cycle. The sound was recorded in late systole and protodiastole at the end of inspiration and the beginning of expiration. It was recorded in mid-systole at the end of expiration and the beginning of inspiration. It was frequently split into two components; sometimes both components were recorded in systole and at other times the second component was noted in protodiastole (figs. 3 and 4). With alteration in the patient's position a change in the character and location of the sound in relation to the second heart sound appeared (fig. 4).

#### DISCUSSION

"Mid-systolic click," a term suggested by Wiedemann (3) and Wolferth and Margolies (2), or "*Le claquement mésosystolique pleuropéricardique*" of Lian and Deparis (4) need not occur exactly in mid-systole. In the majority of cases reported it was closer to the second sound; in many it was equidistant between the first and second sounds; rarely it was nearer the first sound (2, 4, 5). It has been described as "superficial, dry, short and clicking" (2, 4), "extremely clear," and almost always having a rough, clanging, vibrant, sometimes grating ("grinçant") quality (6). In many cases a phasic respiratory variation was noted (4). In 21 cases, Johnston pointed out that the click was more variable with respect to the R wave of the electrocardiogram than was the second heart sound. In some cases it changed in timing, or even disappeared, with varying body position or phase of respiration (4, 5).

The case presented here falls into this classification, with some qualification. That the extra sound may vary to the extent of being recorded in diastole has never been described in the literature, although Lian and Deparis (4) noted that in some cases the sound was followed by a late systolic or early diastolic "souffle." Dr. A. Grishman (7), however, has stated that he has observed two similar cases and was kind enough to show us the records.

The mechanism of the production of this type of sound is not known, although the consensus of opinion is that it is extracardiac. Gallavardin (6) in 1914 reported three autopsied cases of patients with what he called "pseudodoublement du deuxième bruit du cœur." In these cases he found delicate, veil-like pleuropericardial adhesions which he believed were the cause of the third sound. In 1932 he presented a fourth autopsied case (8) with similar adhesions. Lian and Deparis (4) in 1933 reported 50 cases with extra sounds in systole and they were in complete agreement with Gallavardin. None of their cases, however, was autopsied. Johnston (5), in his 21 cases with systolic clicks, also believed that they were extracardiac in origin and that it was difficult to avoid the idea of pleuropericardial adhesions, especially since some of the sounds were influenced by motion, respiration and position.

Groedel and Miller (9) considered this opinion untenable and stated that "it is improbable that pleuropericardial adhesions can produce such heart murmurs." They stated that the pericardium can produce a sound only when there is an extraordinary fixation of a part of the heart, such as is found in calcific pericarditis (pericardial knock). Wolferth and Margolies (2), in view of work done on cadavers, are of the opinion that the view of Gallavardin cannot "at this time be regarded as established."

Although we are unable to solve the problem, we have established that the sound is extra-cardiac for the following reasons: 1. It is not constantly related to any part of the cardiac cycle as determined by simultaneous jugular and carotid pulse tracings and the electrocardiogram; 2. Its position with the cardiac cycle varies under certain circumstances from mid-systole to protodiastole; 3. It is influenced physically by respiration and the position of the patient.

Because this sound appeared after prolonged pulmonary disease we can offer no valid objection to the theory of Gallavardin. It is possible that there are delicate pleuropericardial adhesions or bands in this case. Variation in the tautness and calibre of these bands or adhesions with respiratory motion and change in position may allow for changes in intensity, frequency, splitting and variation in the cardiac cycle, even allowing the sound to go into diastole.

The clinical importance of this sound lies in the fact that it may simulate diastolic gallop rhythm or mitral click. It is generally agreed that the "mid-systolic click" has no prognostic significance and is usually not associated with heart disease. When it is associated with heart disease it is not related to it. More than 80 per cent of the cases reported (2, 4, 5, 6) presented no evidence of heart disease. In most cases there were no complaints referable to the heart and the extra sound was discovered accidentally as in the case reported here. Lian and Deparis (4), however, found that 20 of their 50 patients experienced precordial pain, which was attributed to the pleuropericardial adhesions. This has not been the experience of others. While the patient under consideration may have early cor pulmonale, as evidenced by the elevated venous pressure, rapid circulation time and upright QRS in the right upper quadrant lead (10), the data presented proves that this sound is in no way related to the heart cycle



and therefore may be regarded as extracardiac. Therefore it can have no prognostic significance from a cardiac standpoint.

Since the sound may be heard in diastole and is usually not heard in midsystole it would appear that a less specific term such as "extracardiac click," rather than "mid-systolic click," would be more appropriate.

#### SUMMARY

1. Systolic click is discussed. This third sound of extracardiac origin is reviewed in a case of sarcoidosis.

2. This sound is of no prognostic significance and is important mainly because it may simulate diastolic gallop rhythm or mitral click.

3. No other report has been found in the literature in which this sound was recorded in diastole as well as systole.

4. This sound was loudest at the left 5th interspace parasternally, showed no constant relationship to any phase of the cardiac cycle, varied with respiration and body position, and was recorded in systole and under certain circumstances in protodiastole.

5. The appearance of this sound after prolonged pulmonary disease suggests pleuropericardial adhesions as the causative mechanism.

We are indebted to Dr. A. M. Master for his kind assistance and helpful suggestions in the preparation of this paper.

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# BILATERAL PARASAGITTAL MENINGIOMA WITH RESECTION OF THE ANTERIOR THIRD OF THE SUPERIOR LONGITUDINAL SINUS<sup>1</sup>

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Bilateral parasagittal meningiomas are not very common but when found may straddle one of the large dural sinuses and not infrequently invade and obliterate the sinus. In Dr. Cushing's monograph (1) on intracranial meningiomas there were only 51 parasagittal meningiomas out of a total of 295 tumors of this variety. Of these 51 parasagittal meningiomas, 13 were situated in the anterior portion, 32 in the middle third, and 6 in the posterior third of the superior longitudinal sinus. Only 14 meningiomas were bilateral, and of these 4 were in the anterior third involving the superior longitudinal sinus. Olivecrona (2) reported 205 parasagittal meningiomas, of which 46 involved the anterior third of the superior longitudinal sinus. In a recent report by Francis Grant (3) of 149 cases of meningiomas, 13 were bilateral, involving the anterior third of the superior longitudinal sinus. Complete removal of the meningioma with resection of the involved sinus was carried out in two of these patients, with one fatality.

Parasagittal meningiomas have certain characteristics which are of considerable significance. It has been known for a long time that these tumors produce a hyperplasia of the overlying bone. Neoplastic tissue growing through the Haversian canals of the skull produces a lens-shaped expansion of both tables with characteristic bony radiations by x-ray. A history of local trauma is so frequent in these patients that it must be considered more than an ordinary coincidence. The intracranial portion of the tumor advances so insidiously that members of the patient's family frequently fail to recognize the progressive change. These patients often show changes in personality, euphoria and advancing mental deterioration. Only rarely do they complain of headaches and in the later stages show a degree of untidiness and indifference. If they are fortunate enough to have a generalized or focal convulsion it may lead to early investigation and at times to an earlier diagnosis. As a rule, it is failing vision, too often seriously impaired, that brings about a more searching investigation.

The symptomatology in these cases frequently depends on the relation of the tumor to the Rolandic "point;" that is, the junction of the Rolandic vein with the superior longitudinal sinus. Tumors anterior to this point produce mental symptoms chiefly, whereas tumors posterior to this point will frequently show early signs of paresis and convulsions. The following case report exemplifies the classical symptoms and signs of this type of tumor. The diagnosis could and should have been made earlier, not only by x-ray studies but by simple palpation of the skull. It is also gratifying to report that after complete and radical extirpation of this large tumor with resection of the anterior third of the superior longitudinal sinus, complete recovery followed without any abnormal neurologi-

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cal residua. After a year of comparatively good health this patient, because of local discomfort, had a tantalum plate inserted to compensate for the skull defect.

#### CASE REPORT

*History.* On May 24, 1947, a housewife, aged 54 years, was admitted to The Mount Sinai Hospital complaining of generalized convulsions of five years' duration. These convulsions occurred about three times a week and were often initiated by a peculiar sound in the left ear, as if a "spring" were being snapped. Not infrequently these convulsions were generalized in character but at times were observed to involve the left side of the body. As a rule, with each convulsion she was unconscious for ten or fifteen minutes and there followed a brief period of drowsiness after each seizure. Some of the seizures were accompanied by incontinence. Under luminal and dilantin therapy the convulsions gradually decreased and then for two years prior to admission there were practically none. About



Fig. 1. X-ray film of skull showing characteristic hyperostosis with enlarged middle meningeal grooves.

this time she began to note some numbness of the left side of the face and some parasthesias in the fingertips of both hands occurring several times a day and lasting from one to two minutes. For two years she also noted steady diminution in vision with blurring but no visual hallucinations. Five months before admission she was suddenly seized with a severe left-sided headache accompanied by vomiting and marked diminution in vision. Since then there was progressive weakness, recurrent headaches and vomiting, impaired memory, greater irritability and a slowing in mental activity. This patient presented herself to the Manhattan Eye and Ear Hospital because of failing vision. There bilateral papilledema was discovered and she was advised to enter the hospital immediately.

*Examination* showed a well developed woman, who was slow and indifferent in her reactions, spoke very little, showed considerable memory deficit, and slept a good part of the day. However, she did complain of recurrent severe headaches. Over the right frontal region there was a large, hard nodular lump which did not pulsate and had no bruit. Olfactory sensation was impaired on the right. Visual acuity on the right was 20/25 and on

the left 20/25. There was bilateral papilledema of four diopters elevation with blotchy hemorrhages on both sides. The visual fields were normal. There was also a hypalgesia over the left side of the face and a diminution in sensation in the left cornea. The left arm showed a moderate paresis and there was some clumsiness in movement of the left hand.

*Laboratory data.* Urine and blood examinations were normal. X-rays of the skull (figs.



FIG. 2. X-ray film of skull showing characteristic hyperostosis with enlarged middle meningeal grooves.

1 and 2) showed a hyperostosis of the frontal bone, more marked to the right of the midline. The cerebro-spinal fluid was clear and colorless with an initial pressure of 380 mm. of water, Pandy was 4 plus, and total protein 82 mg. per cent. The electroencephalogram showed a focal lesion, slow growing, in the right frontal area.

*Operation.* Craniotomy on June 6, 1947 was performed under local novocaine anesthesia and intravenous sodium pentothal. Anticipating that in the removal of this meningioma considerable bleeding would be encountered, several units of blood were set aside in preparation for the operation.



A coronal incision was made through the scalp in the frontal area exposing a protruding bony mass. There was bleeding from multiple points in the exposed skull which could only be controlled with bone wax. After making a series of six trephine holes these were joined with gigli saws, and the hyperostosis was completely removed. This exposed the dura and the superior longitudinal sinus in its anterior third. About 6 cm. to the right of the sinus,



FIG. 3. X-ray film of skull showing defect and tantalum repair

a curved incision was made in the dura and when this was retracted typical neoplastic meningiomatous tissue came into view. The dura was similarly opened on the opposite side and it became quite certain that we were dealing with a bilateral parasagittal meningioma anterior to the Rolandic point. Without detaching the tumor from the dura, the neoplastic tissue was gently peeled away from the adjacent normal brain tissue. Bleeding was kept under control with silver clips, coagulation and pledgets of gelfoam. Finally the tumor was freed on both sides and was found also to involve the superior longitudinal sinus and extend downward along the falx to the inferior longitudinal sinus. The involved anter-

ior portion of the superior longitudinal sinus was then isolated, sutured and severed. Gradually the entire tumor with the affected and involved superior longitudinal sinus and the greater portion of the falx in that area was removed. The tumor with the adjacent structures weighed a total of 55 Gm. During the removal of this tumor the patient received

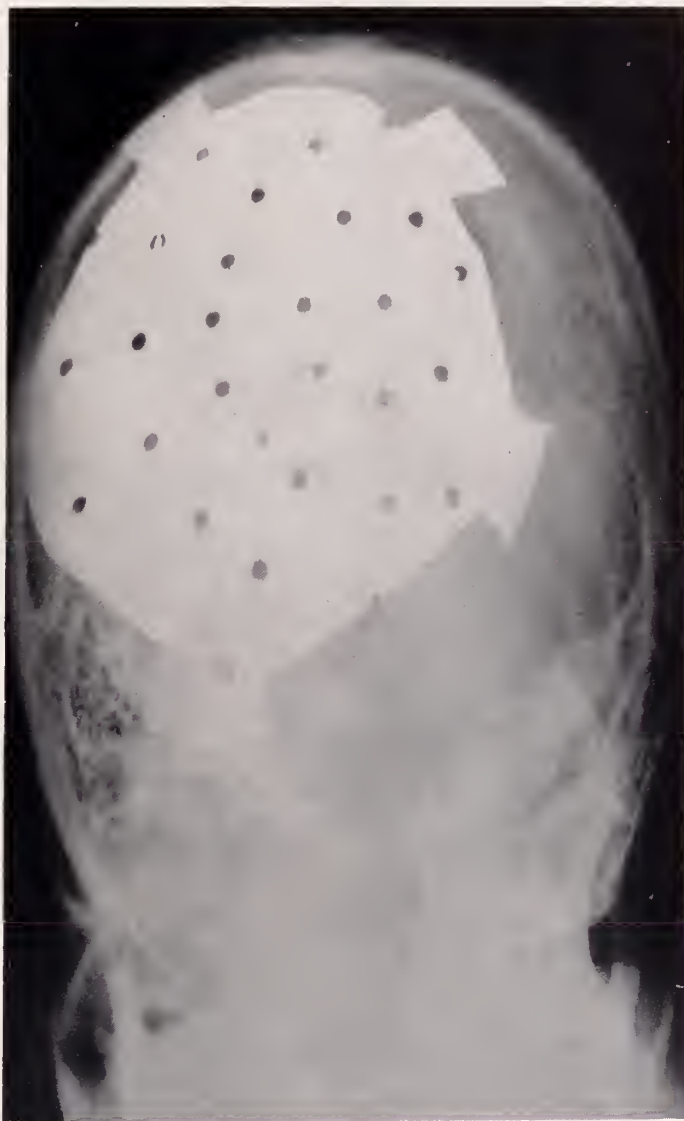


FIG. 4. X-ray film of skull showing defect and tantalum repair

1000 cc. of blood. After all the bleeding was secured, careful inspection of the depth of the cavity showed no remaining evidence of neoplastic tissue. The wound was then closed in the usual manner and the defect in the skull was covered with the overlying flap.

The *postoperative course* was very gratifying. Within a few days she was not only free of headaches but subjectively noted an improvement in personality and in memory. She

was surprised at her interest in people, books and objects about her which she realized had been absent for some time. The wound healed by primary union and seventeen days after operation she was discharged free of symptoms and with considerable improvement in vision. Since then she was able to do her housework without interruption; her only complaint had been a fullness at the operative site. For this the patient was readmitted to the hospital on May 22, 1948. Except for a fluctuant fullness over the skull defect there were no abnormal neurological signs. X-ray films of the skull showed no evidence of neoplastic recurrence. Two days later, under general anesthesia, the scalp over the skull defect was reflected and a tantalum plate inserted (figs. 3 and 4).

Postoperative convalescence was very smooth and the patient was discharged on June 4, 1948, on the eleventh postoperative day, with excellent contour of the skull and with a feeling of comfort and well being.

#### COMMENT

The removal of a parasagittal meningioma, unilateral or bilateral, hardly requires any comment except that to be forewarned about this type of neoplasm is to be forearmed with sufficient blood to combat exsanguination, the usual cause for an operative fatality in these patients. On the other hand, whether or not to resect any portion of the superior longitudinal sinus is deserving of some remarks.

Resection of any portion of the superior longitudinal sinus is a hazardous undertaking. Tragic paralysis, increased mental symptoms and death following resections of portions of the superior longitudinal sinus are not unusual. When and what portion of the superior longitudinal sinus is safe to resect is a difficult decision to make and about this problem there is still considerable difference of opinion.

After reviewing the opinions and experiences of various authors on this subject, the following principles are the most reliable:

1. Before attempting to resect any portion of the superior longitudinal sinus one should be certain whether the sinus is completely obliterated or not.

2. If obliteration of the sinus is only partial, it is then very necessary to know whether the collateral venous drainage is adequate. If cortical veins of sufficient size and patency have to be ligated on the contralateral side, then resection should be avoided.

3. An open venous sinus should never be resected *en bloc*.

4. If obliteration of the sinus is complete, then it should be resected. This is safest when the pathology is anterior to the Rolandic point.

5. Only that portion of the sinus which has become completely occluded should be resected. The adjacent dura and falx when involved in the neoplasm should also be removed *en bloc*. When in doubt about the complete obliteration of the sinus, it is wiser to be content with the removal of only the tumor and postpone resection of the sinus to a later date when obliteration may be more complete and investigation of the sinus less hazardous.

#### CONCLUSION

A patient presenting the classical symptoms and signs of a bilateral parasagittal meningioma is described. Operation included the removal of the neoplasm and

resection of the involved anterior third of the superior longitudinal sinus. Indications and contra-indications for the resection of portions of the superior longitudinal sinus are discussed.

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## INSULIN DYSTROPHY\*

MORTON YOHALEM, M.D. AND HERBERT POLLACK, M.D.

Two years after the introduction of insulin, reports began to appear concerning local atrophy and, less commonly, hypertrophy. The reported incidences varied considerably. Alpert and Ferguson (1) found 7 per cent of atrophy in a series of 430 patients. Marble and Smith (2) reported an incidence of 15 per cent in patients over the age of 20 years and 32 per cent in patients under the age of 20. Wirtshafter and Schwartz (6) reported an incidence of only 1 per cent as did Rosenberger (7), whose series consisted of 4000 patients.

The histopathology of this tissue reaction was studied, and it was universally agreed that it was not truly inflammatory. The grossly atrophic tissues showed disappearance of the fat when examined under the microscope. Hyperplastic fat tissue was seen histologically when the grossly hypertrophic lesions were biopsied.

The different explanations were as numerous as the authors describing them. One suggested that the lipase content of the insulin digested the fat. The preservative in the commercial insulins was indicted. Skin antiseptic agents, it was suggested, were carried into the subcutaneous tissues by the penetrating needle. The needle itself was described as puncturing the thin membranes of the fat cells. It was even suggested that the local fat burned in the flame of the insulin-induced local carbohydrate combustion.

Numerous recommendations were made. Some authors preferred to continue the injections in the same areas; others stated that injections in the affected areas were contraindicated. Good results were reported by using highly concentrated insulins, thereby reducing the injected volume. A return to normal was noted in some patients; the changes persisted or progressed in others.

In view of these divergent reports, it was decided to review the findings in the Diabetic Clinic at the Mount Sinai Hospital. Two hundred and fifty five adult patients with diabetes of sufficient severity to require insulin were selected at random. No patients under the age of 14 years were included in the group. These patients were considered as a representative cross section of the clinic population. Superficial indurations, when found, were not included in the statistics; these were considered to represent non-specific reactions such as are seen in morphine addicts. The positive findings include atrophy of varying degree, hypertrophy, deep indurations of the subcutaneous tissues, and combinations of all three. Using these rigid criteria, 43 per cent of the patients were found to have lesions. Pure atrophy, or atrophy and induration, was found in 33 per cent. Deep induration alone was found in 4 per cent. The hypertro-

\* From the Metabolism Division of the Medical Services of the Mount Sinai Hospital, New York, N. Y. Read before the Clinical Society of the New York Diabetes Association. Seminar Topic of the Metabolism Division.

phies were found in only 3 per cent of this series. The rest were superficial lesions.

*Sex.* Joslin (5) found atrophy most commonly in children of both sexes, occasionally in adult females and almost never in adult males. Marble and Smith (2) reported no males over the age of 20. The literature tends to support this view with its reports of atrophy in females and hypertrophy in males. Our findings did not support this sexual variation. Males made up 30 per cent of our clinic and of our 85 cases with atrophy, 25, or precisely the same 30 per cent were males.

*Distribution of Dystrophic Changes by Duration of Insulin Administration*

DURATION OF INSULIN	SEX	MARKED ATRO- PHY	MODE- RATE ATRO- PHY	SLIGHT ATRO- PHY	HYPER- TROPY PURELY	INDURA- TION	INDURA- TION & ATRO- PHY	SUPER- FICIAL REACTIONS	TOT. WITH CHANGES	TOT. WITH- OUT CHANGES
Under 1 year . . . . .	F	1	2	1				2	6	14
	M	0	0	0				1	1	8
1-14 years . . . . .	F	6	3	7	1	2	2		21	31
	M	0	3	3	1	2	2		11	10
5-9 years . . . . .	F	1	7	9	1	3	2	2	25	24
	M	0	5	3	1	1	0	1	11	9
10-14 years . . . . .	F		4	9	0	1	1	1	16	20
	M		4	0	2	0	1	0	7	5
Over 15 years . . . . .	F		2	2	1	1	1	1	8	12
	M		1	3	1	1	0	0	6	10
Total . . . . .	F	8	18	28	3	7	6	6	76	101
	M		13	9	5	4	3	2	36	42
Per cent of total population . . . . .		3%	12%	15%	3%	4%	3%	3%		

However, some correspondence with the findings in the literature was obtained in two respects. When the degree of atrophy was graded, it was found that all eight cases of marked atrophy were in women. Whether or not this is related to the greater quantity of fat in the female, which would have the effect of deepening the appearance of the concavity, cannot be determined. These patients gave the impression that their fat tissue was of a softer, almost more liquid quality than that of the usual patient. However, none of them were excessively fat. The second significant variation from the general ratio of 3 females to 1 male in the population was in the fat hypertrophies. There were 3 females and 5 males who showed a pure hypertrophy. Of the 7 patients who showed combinations of atrophy and hypertrophy, 4 were female and 3 male.

*Dosage of insulin.* There was virtually no difference in the average insulin

dosage in the group without subcutaneous changes (32 units) from the group with subcutaneous changes (33 units). Surprising, however, was the great difference in the average dose of those with marked atrophic changes; the average of these dosages was 17 units, with the highest of the eight patients using 30 units.

*The degree of control.* Here also, in contrast to the statement that good control of the diabetes would militate against atrophy, these eight patients with the most marked atrophy, as would be expected from the low dosage of insulin required, had rather good control. It was excellent in four patients, good in three, and only one was poor. This case which showed the most marked atrophy in our series, occurred in a very labile diabetic with occasional acetonuria, marked glycosuria and frequent shocks. This agreed with the concept that atrophy may occur in patients whose diabetes was well controlled.

*Location of injection.* The variability of response in the same patient in different areas of his body and in different areas of the same extremity would suggest that it is a local rather than a general factor which makes the patient react to insulin with atrophy, hypertrophy or fibrosis. These variabilities in the type of subcutaneous response were: two patients had marked atrophy of the arms but none of the thighs; one had atrophy of the arms and hypertrophy of the thighs; two had atrophy of the thighs but not of the buttocks; one had atrophy of the medial aspect of the thigh and none of the lateral aspect; four had areas of atrophy and hypertrophy in the same extremity; and one had areas of atrophy, hypertrophy and fibrosis. One patient said that he had given himself protamine zinc insulin in his arms, which were atrophic, and crystalline insulin in his thighs, which were hypertrophic.

Joslin (5) reported that he had seen atrophy distant from the sites of the injections (face, submental region and breast). In this respect our findings agree with those of Wilder who could not discover these distant reactions.

*Age of patients, duration of diabetes and years of insulin.* A comparison of the age of the patient and the duration of the diabetic state in those with changes and those without them, revealed only that those with changes averaged some few years younger. An analysis of the duration of insulin usage was made. In general it was the same in the two groups. In the marked atrophy cases the mean length of insulin usage was 7-8 years. The longest duration of insulin administration of the marked atrophy cases was only six years, with an average of  $3\frac{1}{2}$  years. This is in contrast to the findings in the cases of hypertrophy which were evenly distributed from 1-15 years of insulin usage.

*Depth of the injection.* All patients used the same size needles. They were asked whether they inserted the needle obliquely (which perhaps represents a superficial injection) or perpendicularly (which results in a deeper injection). It is difficult to determine whether or not this represents a factor in the production of the fatty changes. In the group without subcutaneous changes, 56 per cent described their injection as perpendicular; of those with changes only 30 per cent described them as perpendicular. In the group of patients with marked or

moderate atrophy, twice as many used the oblique technique as used the perpendicular one. These figures seem statistically significant. Consequently, the deeper the injection the less likely the development of fat changes.

*The development of the lesion under treatment.* Reports in the literature vary as to what to do with subsequent injections once the fat change has appeared. Alpert and Ferguson (1) reported that in some patients injections were continued in the same areas and that although atrophy persisted it did not increase or extend; consequently, their recommendation was to continue in the same area and not to expose other areas to the dangers of dystrophy. Wirtschafter and Schwartz (6) reported that with continuation of injections restoration of the fat occurred, associated with some weight gain and better control of the diabetes. Joslin recommended the avoidance of the dystrophic areas and maintained that in a fair percentage redeposition of the fat will occur. Adlersberg (3) reported that with cessation of injections hypertrophy continued. In brief, recommendations have been made to avoid the area, to continue in the areas so as not to endanger other parts of the body, and to continue the injections in the areas so that the fat may be reconstituted.

Our observations confirmed only the variability of the course of the lesions. One patient had reconstitution of fat of his arms since cessation of injections there, although slight atrophy of the thigh is now present; one patient with hypertrophy of both thighs said that he had had hypertrophy of his arms which had disappeared with cessation of injections. Perhaps the best answer we can give is that the percentage of patients with changes reached their peak in the group taking insulin for 5-9 years (over 50 per cent of this group had fat changes), and then gradually fell off to 38 per cent. All the marked atrophies were in those taking insulin less than 6 years. These two observations may indicate the tendency for the fat to be reconstituted, no matter what program is followed.

*Associated diabetic complications.* The incidence of hypertension, diabetic retinopathy, diabetic neuropathy, coronary arteriosclerosis of clinical magnitude, peripheral vascular disease, and gall bladder disease was equal in the series of patients with changes and those without. There was a slight increase in the incidence of clinically significant cataract in those with changes but it is probably of no significance: 14 per cent of those with fat changes and 10 per cent of those without fat changes. Allergy to insulin probably plays no part in the production of the changes since general symptomatic allergy was present in none of the patients with fat changes and in 4 per cent of those without them. There was one case of allergy to insulin in each series.

*Clinical significance of the lesions.* The cosmetic importance of the lesion need only be mentioned. Goldner (10) reported two cases of hypertrophy in which the insulin effect of lowering the blood sugar was less when the insulin was injected into areas of hypertrophy than when injected into normal areas. Joslin (5) cited several cases in which the same dosage of insulin injected into normal areas instead of the dystrophic area caused insulin shock. Apparently there is



some interference with absorption of the insulin in the dystrophic areas. We made no studies of this. There is some tendency for the patient to use the old areas because repeated injections in the same area dull the pain of the needle.

*Summary.* Before summarizing in an effort to find some of the common factors, we should first cite Blotner's (4) most interesting case of a young woman without diabetes but who received ten units of insulin before each meal for malnutrition. The insulin was taken for three weeks. Four months after stopping insulin, atrophy appeared in the right thigh, where she had taken twice as many injections as in the left. The atrophy persisted for  $2\frac{1}{2}$  years and during pregnancy, when she gained weight, the atrophy was more noticeable. This would

#### *Associated Diseases*

Patients without changes.....	93	Patients with changes.....	83
Cataracts.....	10	Cataracts.....	11
Hypertension.....	39	Hypertension.....	25
Arteriosclerosis.....	34	Arteriosclerosis.....	27
Neuropathy.....	8	Neuropathy.....	7
Retinopathy.....	23	Retinopathy.....	18
Peripheral vascular disease.....	12	Peripheral vascular disease.....	16
Allergy to insulin.....	1	Allergy to insulin.....	1
Tuberculosis.....	2	Tuberculosis.....	0
Lues.....	3	Lues.....	0
Carcinoma.....	2	Carcinoma.....	0
Graves.....	1	Graves.....	2
Gallstones.....	1	Gallstones.....	2
Xanthomatosis.....	1	Thyroid Adenoma.....	1
Keratitis.....	1	Parkinson.....	1
Epilepsy.....	1	Liver enlargement.....	2
		Dacryocystitis.....	1
		Iridocyclitis.....	1
		Peptic ulcer.....	2

indicate that diabetes mellitus is not necessary for the peculiar reaction of fat to insulin.

Most of our findings were negative. Comparison of age, sex, duration of insulin administration, dosage of insulin, degree of control, and location of injections revealed no differences in those with fat dystrophies and those without dystrophies. In these two groups there was no difference in the incidence of associated diseases or degenerative changes and these seemed to play no part in the production of the dystrophy.

These were the positive findings: (1) The patients with the most marked atrophies were women; their diabetes was mild, easily managed, and they had been taking insulin a relatively short time, none more than 6 years. (2) A higher percentage of the patients with skin changes were using an oblique technic than those without skin changes. (3) There seemed to be support both in the

history of the individual patients and in the decreasing incidence in the diabetics of longer duration for the theory that regardless of whether or not the injections were continued in the same site, the lesions, at least in some cases, reconstituted themselves.

The cause of the changes seems to be, viewed in the light of individual variation, a local quality of the fat tissue.

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## SPECIFIC TREATMENT OF RHINOSCLEROMA WITH STREPTOMYCIN\*

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Rhinoscleroma is a chronic, specific, granulomatous infection of the upper respiratory tract due to *Bacillus rhinoscleromatis* and common in the lower classes of unhygienic environment in central Europe and Italy. It has been reported in northern United States, usually in the foreign born although cases in native Americans have occurred. We may expect more after the migration of people in the post war period.

Predominantly affected in this disease are the nose, nasopharynx, palate, larynx, trachea, and bronchi. Gross features of involvement in rhinoscleroma are the appearance of hard, infiltrated granulomatous tissue, intermingled with areas of atrophic mucosa. This mucosa is usually covered by crusts with fetid odor. Removal of these scabs is often followed by bleeding.

The *Bacillus rhinoscleromatis*, which is pathognomic of the disease was first described by Von Frisch. The organism is a gram negative bacillus, usually assuming the shape of plump rods with well rounded ends. They are mostly intracellular within the foam cells, but may be seen extracellular after the rupture of the cells. The organism may be a strain of the *Bacillus mucosus capsulatus*.

No specific treatment of rhinoscleroma has heretofore been employed. The various therapeutic measures which have been recommended include: surgical extirpation, irradiation, Fuadin and Chaulmoogra oil. In spite of the fact that in many instances, a combination of these drugs and irradiation were used, cure of the disease is rarely attained. Symptomatic relief and temporary arrest of the infection has been the general rule.

Esteban Reyes (1) reviewed his personal experiences with two hundred cases of rhinoscleroma and obtained surprisingly good results through intramuscular injections of Azosulfamide plus Roentgen rays.

Recently Hara, Praft, Levine and Hoyt (2) published a detailed study of seven cases of Rhinoscleroma occurring in one family, all born and raised in Colorado. In two cases, the patients were treated with Streptomycin 2 Gm. daily and  $\frac{1}{2}$  Gm. by aerosol. In one instance, the *Klebsiella Rhinoscleroma* could not be recovered after the sixth day of treatment, but in the other the bacillus has not been eradicated.

Devine, Weed, Nichols and New (3) reported a case of chronic granuloma of the upper air passages, probably rhinoscleroma. On culture of the granulomatous material, large numbers of *Klebsiella* were obtained. The patient received 97.25 Gm. of Streptomycin and made a good clinical recovery.

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## CASE REPORT

*History.* Patient is a forty year old, white male who was born in Poland and migrated to this country at the age of six. For the past ten years, he has been troubled with dryness and crusting of his nose and throat. Three years ago, his nose started to become obstructed with foul smelling scabs and he became hoarse. This progressed to almost complete aphonia at times, until a coughing spell would clear his larynx of secretion. He had intermittent stridor and on one occasion, marked dyspnea on slight exertion. Six months previously, he almost choked until he succeeded in bringing up a scab from his larynx. A submucous resection was performed several years previously without improvement. He managed to get some relief by nasal insufflation of normal saline. Anosmia developed, followed by the loss of considerable weight.

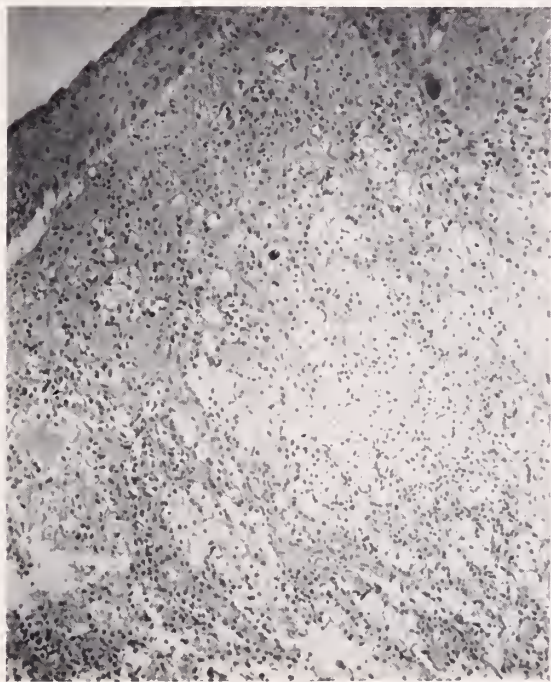


FIG. 1. Section from the nose showing metaplastic epithelium and numerous Mikulicz cells. Several hyaline Russell bodies are seen in a stroma of round and plasma cells. Mikulicz or so-called Foam cells are large, vacuolated cells with a clear zone of cytoplasm and small pyknotic nucleus.

Several months ago, he was hospitalized at another institution where he was bronchoscoped. Following this procedure, he had considerable labored breathing which cleared up spontaneously. His condition grew progressively worse and he was now admitted to a local hospital in New York City. The clinical diagnosis of rhinoscleroma was made there and this was substantiated by microscopic examination of a biopsy from the nose and larynx. He was referred to the Mount Sinai Hospital, New York City, for treatment.

*Physical examination.* On admission to Mount Sinai Hospital, on March 10, 1947, examination revealed a well developed male, in general good condition. He spoke with a raspy, hoarse voice, had marked nasal obstruction and was beset with a foul odor. Intranasal examination revealed the presence of thick, yellow, foul smelling crusts in both nasal fossae. Upon removal of these scabs, the inferior turbinate appeared somewhat



atrophic. The middle turbinates were replaced by thick, granulomatous tissues which crowded the nasal septum bilaterally. There was a small, septal perforation anteriorly. The nasopharynx was covered with thick, brownish crusts. On indirect laryngoscopy, the arytenoids appeared edematous. The false cords were indurated and granular and covered with crusts, similar to that present in the nose. The true cords were thickened and showed only a limited range of motility. There was no cervical adenopathy. In addition, there was a subglottic, irregular infiltration narrowing the glottic chink to about 3-4 mm.

The Department of Pathology examined the slides of biopsies taken from the nasal mucosa and larynx. Both demonstrated the characteristic, pathologic findings of Rhinoscleroma (fig. 1).



FIG. 2. Roentgen film showing shadow at right hilus due to infiltration in right upper lobe.

Roentgen examination of the paranasal sinuses showed a moderate thickening of the lining membranes of the right frontal sinus. Both antra were considerably cloudy, more marked on the right.

X-ray examination of the chest showed a patch of infiltration which extended from the right hilum, laterally, into the mid-third of the lung field (fig. 2). On lateral view, the short fissure was bent upward, indicating partial collapse of the anterior segment of the right, upper lobe, secondary to the chronic disease.

On admission, cultures were taken separately from the exudate in the nose and larynx. In both instances, a gram-negative bacillus of the Friedlander Group was isolated and identified as the *Bacillus Ozena* of rhinoscleroma. Susceptibility of the bacterium to Streptomycin and Penicillin were now determined. To Streptomycin, the bacillus was one times as resistant as the standard strain, whereas to Penicillin, the resistance was more than 2,000 times as much.

*Course.* One week after admission, March 17th, the patient was started on Strep-

tomyacin, receiving 0.5 grains, every six hours, parenterally. After three days of therapy a moderate improvement in the appearance of the nose and larynx was noted. After eleven days of treatment, the larynx showed continued improvement but crusting was still present in the nose. Penicillin aerosol 50,000 Units q.i.d. was administered in an attempt to clean up the secondary infection.

Three weeks following the administration of Streptomycin, a marked improvement in the appearance of the mucosa of the nose and nasopharynx was apparent. The intranasal granulomatous mass had disappeared. Some adherent crusts were still present but upon removal of these, an intact somewhat atrophic mucosa could be seen.

The laryngeal picture was strikingly changed. The subglottic infiltration had markedly subsided. The granular induration of the false cords had vanished to a great extent but motility of the vocal cords was still limited. Daily instillation, into the larynx of warm saline was begun.

One month after therapy, a bronchoscopy was performed with a seven mm. tube. A considerable amount of dried secretion of the tracheal wall was encountered. Stringy mucous was seen coming from the right upper lobe bronchus. Smears and cultures were repeated from the larynx and trachea but were negative for *Bacillus Rhinoscleroma*. Streptomycin was discontinued after thirty-seven days of therapy. Cultures at irregular intervals were repeated from the nose and nasopharynx and larynx and failed to show the *Bacillus Rhinoscleroma*. He was discharged on May 1, 1947.

*Comment.* A patient with ulcero-granulomatous lesions in the upper air passages is presented. Biopsy from the larynx and nose revealed the characteristic pathology of rhinoscleroma with preponderance of Mikulicz or Foam cells. On bacteriological study of the exudate from the nose and larynx, the *Bacillus* of rhinoscleroma was isolated in large numbers. Susceptibility of the bacterium to Streptomycin was one times as resistant as the standard strain. The stenosis of the larynx was so advanced that tracheotomy was seriously contemplated. Streptomycin was administered for thirty-seven consecutive days for a total of 97.4 Gm. Six months after cessation of intranasal treatments, examination failed to show any granulomata but the mucosa was somewhat atrophic. Direct laryngoscopy revealed only slight, residual scarring but no evidences of specific disease. The airway was practically normal. Cultures from the exudate were negative for the *Bacillus rhinoscleromatis*.

The patient has remained symptom free to date, one year after the institution of Streptomycin therapy.

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## NOTES ON THE EARLY HISTORY OF LEUKEMIA\*

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At a hematological meeting on leukemia it is appropriate to present a retrospective survey of this still puzzling condition, especially since the time almost coincides with the centenary of the first descriptions of leukemia.

The origin of modern hematology is closely related to the first steps in microscopy as applied to medical sciences. It may be asked why, after Leeuwenhoek's discovery, two centuries were necessary for medicine to recognize the significance of the microscope, when entomologists, for instance, had already derived great advantages from its use for many years.† Medicine during the 18th and at the beginning of the 19th century was held within the confines of rigid systems, blocking any innovation coming from outside of the framework of the system. One is amused today by the arguments of the doctrinaires of that day in their fight against the innovators. Their debates have a strangely antiquated turn, but these discussions were as genuine as ours and their slogans proved as efficient as many a suggestive catchword employed today. Against the microscope they spoke of "chimerical vision" or "optical illusions." In the opinion of a trustworthy observer (1) of this time the formula of the "optical illusion" delayed for many years the introduction of microscopy as a complement to medical studies.

These circumstances permit the evaluation of the merit of Alphonse Donné who, despite obstinate bias and the active hostility of his colleagues and of the Parisian medical faculty, dared to organize in 1837, at his own expense, a course on clinical microscopy. Donné is rightly credited with the first observation of leukemia (2).

The patient was under the care of Barth on the service of Chomel at the Hotel Dieu. "The patient, a 44 year old housewife, entered the Hospital on June 26, 1839. Seventeen months previous to her admission she had given birth to a dead child; and soon after, a tumor appeared in her abdomen. Six weeks before admission she became deaf and she came to Paris to be treated for the tumor and the deafness. On examination a tumor was felt in the left hypochondrium, the upper end of which was situated below the left hypochondrium, the lower extremity reaching the inguinal fossa. The medial border almost reached the linea alba. This border could be easily circumscribed on palpation and showed distinct indentation a little below the umbilicus. The surface was smooth, of firm consistency and was dull to percussion. A week after admission the patient experienced cramps followed by numerous watery stools mixed with bloody mucus. Despite the administration of opium these abdominal symptoms continued and

\* Read before the Society for the Study of Blood, at the New York Academy of Medicine, on November 20, 1947.

† Exceptions are: Albrecht von Haller in "Elementa Physiologiae Corporis Humani" II, 34 (1757); William Hewson in "Figure and Composition of the Red Particles of the Blood Commonly Called Red Globules" in *Philosophical Transactions* (1773).

on the 14th of July the patient died. An autopsy was performed 23 hours after exitus occurred. On the same day a portion of the blood taken from the corpse was brought to Dr. Donné. Here is the letter which this skilled observer wrote:

"The blood you sent me, my dear colleague, shows a remarkable change and, most conspicuous, despite the fact that it had been collected under unfavorable conditions, *id est*, from a dead body. More than half of the cells were "mucous globules." This fact needs perhaps some explanation. You know that normal blood contains three types of cells: 1. Red cells—the essential cellular constituent of the blood. 2. White cells or mucous cells (which I consider as being secreted from the vascular wall). 3. The small globules.

"It is the second variety which dominates so much, that one wonders, knowing nothing about the clinical course, whether this blood does not contain pus. As you know, the pus cell cannot yet be differentiated, with definite accuracy, from mucous cells."

Donné had the opportunity of observing another case—this one *in vivo*. He reports it in one of his lectures collected in his treatise on microscopy, published in 1844 (1): "There are conditions in which the white cells seem to be in excess in the blood. I found this fact so many times, it is so evident in certain patients, that I cannot conceive the slightest doubt in this regard. One can find in some patients such a great number of these cells, that even the least experienced observer is greatly impressed. I had an opportunity of seeing these in a patient on the service of Dr. Rayer at the Hospital de la Charité. This man, who was in the prime of life, was affected with arteritis, especially in the vessels of his legs. Both legs were the site of ecchymoses, gangrenous blisters. The blood of this patient showed such a number of white cells that I thought that his blood really was mixed with pus, but at the end I was unable to observe a clear-cut difference between these cells and the white cells. At autopsy there was no trace of pus in the vessels or in the interior of the clots."

Donné in his treatise on microscopy mentions proudly how many foreign students followed his lectures and demonstrations. At that time Paris in general as well as medical Paris was an exciting attraction. "Every science is progressive," wrote Henry J. Bowditch in the June 1841 issue of the Boston Medical and Surgical Journal, "especially is this true in France where there is more intellectual activity at the present time than in any other country."

Among the foreign students was a twenty-five year old Scottish physician whose name was John Hughes Bennett. In a lecture published in 1841 in Edinburgh "On employment of the microscope in medical studies" (3) Bennett stated that he attended "the public instructions given by Mr. Donné of Paris" and he also gave credit to Donné's "perseverance and enthusiasm" in overcoming the many obstacles involved in a course in clinical microscopy. It was Bennett who published in 1845 (4) a case report on "Hypertrophy of Spleen and Liver" in which leukemia was first given recognition as a clinical entity.

A 28 year old slater was admitted into the ward of the Royal Infirmary on February 27, 1845. Twenty months before admission he had experienced great



listlessness on exertion. Eight months previous to hospitalization he had noticed a tumor in the left side of the abdomen which gradually increased in size. It was never painful. Other tumors appeared in his neck, axilla, and groins. After a short episode of diarrhea, accompanied by fever, the patient died suddenly on March 15 of the same year. At autopsy the spleen and liver were found considerably enlarged. The lymphatic glands were everywhere much enlarged; in the groin they formed a large cluster, some being nearly of the size of a small hen's egg, and several being that of a walnut. The axillary glands were similarly affected. The bronchial glands were not only enlarged, but of a dark purple color. No pus was found in any of the tissues.

Microscopic examination revealed that "The yellow coagulum of the blood was composed of coagulated fibrin in filaments, intermixed with numerous colorless corpuscles. The corpuscles were round, their cell wall granular and presented all the appearance of pus corpuscles. The enlarged lumbar glands on being pressed exuded a fluid that was crowded with corpuscles, some resembling the colorless corpuscles already alluded to; others oval and round containing a distinct nucleus."

In his comment Bennett insisted that neither abscesses nor purulent infiltration of any tissue was present, and added: "No observation having been made on the blood during the life of the individual, it was impossible to say how long that fluid had contained the excess of colorless corpuscles which were found in it after death; but I believed at the time that they were formed towards the close of life, and probably when fever became manifest."

A similar conclusion was arrived at by Dr. Craigie from his observation of this case. He had published earlier in the "Edinburgh Journal of Medicine and Surgery" (64:400, 1845) a "Case of disease of the spleen in which death took place in consequence of the presence of purulent matter in the blood." The case had been observed in 1841 and Craigie already then suspected that "the globules of purulent matter and lymph" came from the spleen. "If these did not come from the spleen," he ventured, "it is impossible to see whence they did come."

It is obvious that the observers of this first group still were haunted by the idea that they were dealing with some pus-forming condition.

Under the title "White Blood" Rudolph Virchow in 1845 (5) published a case report concerning a 50 year old woman. She was admitted to the Charité Hospital of Berlin because of great loss of weight, severe coughing, swelling of the lower extremities and frequent bloody stools. On examination, a marked enlargement of the spleen was found. The patient developed severe epistaxis and died five months after admission to the hospital. At autopsy an enormously hypertrophied spleen was found. The microscopic examination of the content of blood vessels showed mostly white corpuscles and a few red corpuscles. Of interest are his observations, some of which follow:

"The relationship between the pigmented and colorless blood corpuscles seemed to be the rule and the red corpuscles a kind of exception. When I therefore speak of white blood, I mean in fact a blood in which the proportion between the

red and white blood corpuscles is reversed, without noting any mixture of strange chemical or morphological elements.

“Considerations: It would be premature to draw sweeping conclusions from a single case, so unusual, since the relationships are not so clear and the history of the disease contains so many gaps. The older accounts of white blood are quite useless because microscopic examination is lacking. They relate mostly to loss of blood by hemorrhage, fasting, etc. Now it is further known since Hippocrates, that the diseases of the spleen rather frequently cause epistaxis. In the present case we can construct the following etiological succession: splenic tumor, nosebleed, white blood. The persistence of the cough and diarrhea was not due to local lesions, as well as the hydropic infiltration; the nosebleed, the furuncular and pustular eruption, are all to be considered as signs of increasing dissolution of the blood. The excessive formation of white blood cells (lymph corpuscles) cannot be explained by increased flow of chyle, since chylickation is not especially active in the presence of diarrhea, but this all speaks for an increased formation of the cells in the blood, which suggest a great mass of small molecules (primary nuclei). Also, it should not be overlooked that the cough, diarrhoea and edema were present before the nosebleed, and that the remarkable change of red blood into white blood could only have taken place quite recently, because the blood from the epistaxis was always red.”

In the first volume of his famous *Archive*, 1847, Virchow reviews the problem of leukemia (6). In his introduction he says: “There are certain truths which, in the field of science, receive recognition only very slowly and step by step. This seems to be the case with my publications on white blood . . . and its relationship to chronic enlargement of the spleen.” (Hienle called this introduction “pompous.”) In the same paper Virchow reported a case history of a patient with generalized adenopathy; the post mortem blood examination revealed a striking increase in white cells, in the ratio of white to red cells as 2:3. This case seemed to the author of particular interest in view of the absence of any etiological factor such as scrofulosis, typhus, malaria or any exanthematous disease. He concluded that: “We have therefore provisionally to consider this condition as a primary, autonomous or, as we say, substantive disease of spleen and lymph nodes, which directly produced an increase of white cells of the blood.”

Two years later, in 1849, Virchow’s understanding of the new disease and of the blood had grown markedly as shown by the statement that: “The blood as a transitory tissue, with fluid intercellular substance, continually receives young tissue elements, called cells. Under normal conditions the overwhelming majority develop into specific blood cells, the hematin-bearing red corpuscles. Under abnormal conditions a developmental disturbance takes place which hampers the formation of the specific blood element, while the development of young cells as non-specific simple cells is favored. These cells are the so-called colorless blood corpuscles or lymph-corpuscles.”

An account of the vehement priority controversy between Virchow and Bennett is omitted here because it would take one too far afield. However, it may

be mentioned that Virchow was angry at Bennett for having failed to quote him. He blamed the Scots for "the free and easy appropriation of other men's intellectual products." The reply of Bennett was that of a political antagonist: "I must be excused from entering into literary warfare with revolutionary combatants, whose chief weapons are detraction and attacks on character."

In a highly interesting debate on leukemia which lasted during six consecutive meetings at the Société Médicale des Hôpitaux de Paris from December 12, 1855 (7) up to February 27, 1856 leading physicians of France such as Lasègue, Barth, Gubler, Woillez, Becquerel and Trousseau expressed their views. The *pro* and *con* of this discussion contained many facts which are now considered as definite acquisitions in the understanding of this disease.

Amazing statements are recorded, worthy of being recalled. What were the arguments of those who spoke against leukemia as a disease entity? Barthézy gave the best summary of this point of view: "Leukemia is a cachexia and a cachexia is a deterioration of the whole economy (*totius substantiae*) following chronic conditions. Leukemia is nothing but a change of blood, only instead of a diminution of one of its constituents, we find an increase."

This theoretical argument was almost a matter of pure semantics. Another argument, no less retarding the progress of science was the fact that the condition labelled leukemia had many features in common with malaria, such as fever, splenomegaly, anemia. It was held by some that "Leukemia is therefore nothing but a special form of malarial cachexia. The ineffectiveness of quinine proves only that the patients had reached the state of cachexia against which all remedies will fail."

The arguments acquired an almost factional character and were further complicated by poetical quotations. It needed much courage to defend the disease as a new entity. The danger of discredit was looming for those who dared counter the well-entrenched traditions of a conservative majority.

Among these dauntless men, three stand out: Barth, Vigla and Gubler. Trousseau was on their side. Gubler adopted a standpoint of prudent moderation, which should be considered in the light of the idea of the "juste milieu"—the golden mean which was still prevailing in that epoch. He maintained that: "Before we can establish a definite theory of leukemia we will have to collect pathological observations for a long time, we will have to analyze them cautiously and only after having collected, compared and exactly evaluated them, will we be able to deduce logically the cause of this excess of white cells and its significance, either as a distinct disease or as a morbid element common to diverse cachexias."

This sounds like a motion of postponement in parliamentary maneuvers, and Gubler seemed to use the tactics of compromise only to avoid a clash with the opponents. On May 11, 1859 he published a case report entitled "A sudden increase in white cells in the final state of cachexias." A 21 year old boy apparently had attacks of malaria contracted in North Africa. Suddenly before death he developed a tremendous increase in white cells, 30 to 50 times normal.

"We deal here," he stated, "with a kind of acute leukemia. . . ." Although this case may not have been a case of leukemia, Gubler's contribution to the vocabulary is noteworthy.

The autonomy of leukemia was most clearly supported by Vigla: "Leucocythemia is the first condition discovered with the microscope at the bedside. The blood changes constitute the principal character, fundamental to this disease. But the symptoms are so characteristic, follow so regular a course, that I was able to reach a diagnosis before I examined the blood—a diagnosis which was confirmed microscopically. I was impressed by the great resemblance of three facts I observed. I found the characters of a special malady in the uniformity and regularity of the morbid phenomena.

"This condition is sufficiently characterized by its anatomical changes, its symptoms and its course:

"1. Anatomical changes

a. The white cells are increased in a considerable proportion, 25-30 for 100 red cells

b. Spleen—enlarged

Liver—enlarged in two-thirds of observed cases

Lymph nodes frequently enlarged

(Thyroid, suprarenal glands may be enlarged)

Blood examination shows:

Diminution of its specific gravity

Increase in fibrin

Reduction of red cells

Reduction of albumin

Reduction of iron

Increase in water

2. Most striking (clinical) features

Anemia

Weight loss

Cachexia

3. Course: Three periods

a. Splenomegaly accompanied often with hepatomegaly and lymphadenopathy: anemia, dyspnea, weakness

b. Febrile course—profuse perspiration

c. Diarrhea, hemorrhages

The average duration from the day splenomegaly has been observed, 14 months to a maximum of 4 years—minimum 3 months."

Vigla met objections called against his views by the following arguments:

"Malaria: There is doubtless some relationship between leukemia and malaria. We made thorough investigations and found these circumstances only in exceptional cases. In a definite case of leukemia, malaria is only a coincidence and at the most a predisposing cause. In Paris, where my patients had lived for many years, there is no malarial cachexia severe enough to lead to exitus.

"Leucocythemia a change common to all cachexias: Although cachexias are frequent, leucocythemias are rare and are found only associated with glandular hypertrophies, such as spleen, etc. There are few diseases with such striking an individuality than the one we are dealing with. . . ."



I may be accused of having given a microscopically detailed account of minute events. However it should be borne in mind that out of these tiny germs grew our present-day knowledge, and that what we know about leukemia is still too fragmentary to allow us to look haughtily upon the early gropings. The great Ernest Renan (8) wrote in 1849 almost prophetically: "What can surprise us if we consider that all progress accomplished up to now is perhaps only the first page of a preface of an infinite work?"

Virchow cleared the way for the understanding of leukemia as a disease *sui generis*. But a century after his first publications we are still searching for an understanding of the condition. History in its course has removed many obstacles providing highly valuable technical improvements. As to the future, the historian fortunately has only to question the past in order to grasp the present, the future is beyond his goal.

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THE FUNCTIONAL SIGNIFICANCE OF THE VARIOUS LEUKOCYTES  
IN INFLAMMATION<sup>1</sup>

WILLIAM E. EHRLICH, M.D.

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Our concept of inflammation has greatly changed during the last century. Whereas formerly attention was focused on the circulatory phenomena which dominate the clinical picture, we now recognize that the vascular response is merely a preliminary reaction designed to deliver certain leukocytes and to stimulate the production of others. The essential phase of inflammation is concerned with the destruction of antigen and the synthesis of antibody. It is a biochemical phenomenon due to the action of the enzymes contained in the various leukocytes. It takes place in the regional lymph node as well as on the field of inflammation. The leukocytes which cause destruction of antigen are the granulocytes (polymorphonuclear leukocytes) and the macrophages (monocytes, reticuloendothelial cells), the cells which synthesize antibody are lymphoid cells (plasma cells); the role of the lymphocytes is not yet certain.

## GRANULOCYTES AND MACROPHAGES

The first leukocytes which appear on the field of inflammation are usually the neutrophile or, in rabbits, the pseudoeosinophile granulocytes, and the macrophages. In the beginning granulocytes predominate apparently because in the blood they outnumber the monocytes about 10 times; also they are more chemotactic (1). After 3 days or later macrophages preponderate because the granulocytes disintegrate rapidly leaving longer-living cells behind. In later stages of inflammation plasma cells and lymphocytes may prevail; they are the outstanding feature of unspecific chronic inflammation (round cellular infiltration).

The function of the neutrophiles, pseudoeosinophiles and macrophages in inflammation has been known since Metchnikoff (2). It is phagocytosis (ingestion) and splitting (digestion) of particulate matter such as bacteria, fragments of tissue or dust particles. As the smaller granulocytes were found to phagocytose small particles, while the larger macrophages ingest large fragments also, Metchnikoff spoke of microphages and macrophages.

The mechanism of phagocytosis has been well discussed by Mudd, McCutcheon and Luké (3). It has been shown that ingestion depends on interfacial tensions between phagocyte, particle and surrounding medium. Whether or not phagocytosis occurs depends mainly on the nature of the surface of the particle.

<sup>1</sup> Presented as the first of the series of lectures on recent advances in Pathology and Bacteriology at the Blumenthal Auditorium, The Mount Sinai Hospital, New York, December 22, 1948.



Digestion of the ingested material is due to enzymatic action. The enzymes which occur in the *neutrophile* and *pseudocosinophile granulocytes* have been well enumerated by Barnes (4). There are nucleases which split nucleoprotein into nucleic acid and protein. As the nucleic acids lose their staining reaction during digestion in the cell, it is reasonable to assume that there are nucleotidases and nucleosidases as well. In fact, the demonstration in neutrophiles of adenosinase and amylase suggests that these cells may also digest split-products of nucleosides. It has further been shown that the *neutrophiles* of carnivores such as cats, dogs and man are rich in trypsin which splits protein into polypeptides and amino acids. The *pseudocosinophile granulocytes* of the herbivorous rabbit do not contain trypsin; instead, they are rich in lysozyme, a carbohydrase which is believed to lyse bacteria by hydrolysis of their water-insoluble polysaccharides.

The *macrophages* also contain nucleases, proteinases and carbohydrases as shown by the fact that they digest protein and carbohydrate containing microorganisms. They differ from the granulocytes in that they are rich in lipases as first demonstrated by Bergel (5). This quality enables them to digest bacteria with a lipid capsule such as tubercle and leprosy bacilli which can be ingested, but not digested by granulocytes.

It has been found that the high molecular compound attacking enzymes of the granulocytes and possibly also of the macrophages act best in a slightly alkaline medium, whereas the lower compound attacking enzymes such as adenosinase and amylase are most effective in a slightly acid medium. It has further been observed that trypsin does not readily attack serum globulins unless they have been denatured (6). Recently, the splitting of corpuscular antigen in inflammation has been tested in vivo (7). Intact sheep erythrocytes and dysentery vaccine were injected into the foot pad of rabbits, and the resulting exudate at the place of injection, the lymph draining from this area, and the regional lymph node were analysed for the presence of soluble material of the same antigenic specificity as the cells injected. It was found that soluble antigen appears on the field of inflammation within half a day after injection, it attains a high level during the following two days, and it falls off gradually thereafter. In the lymph node it disappeared on the 3rd or 4th day when antibody made its first appearance. These various observations seem to show that the splitting in the intact granulocyte and probably also in the macrophage does not go very deep. In the case of corpuscular antigen, the granulocytes and macrophages elaborate a soluble antigenetically active material; they merely prepare the antigen for its chemical action.

It has been claimed that the digestion of bacteria and other antigenic materials by granulocytes and macrophages resulted in the production of antibody by these cells. In fact, the reticuloendothelial theory of antibody formation is still widely sponsored in the main apparently because the output of antibody may be depressed through blockage of the macrophages with phagocytotic material such as iron sugar, india ink, trypan blue or collargol. It has been pointed out elsewhere (8) that experiments of this type show merely that crowding of phagocytes with particulate matter interferes with ingestion and digestion

of additional material. In vivo studies of antibody formation by granulocytes and macrophages in the foot pad and the peritoneal cavity of rabbits injected with typhoid or dysentery vaccine failed to show antibody formation by these cells (9). The titers obtained from extracts of these cells during the period of antibody production were usually less than 1:32, whereas in the regional lymph nodes they were 60 times as high. By injecting antibody intravenously and an unspecific irritant intraperitoneally, it was shown that the low titers on the field of inflammation are fully explained by secondary concentration here of antibody from the blood stream.

These various observations are interpreted to signify that the neutrophile and pseudoeosinophile granulocytes and the macrophages function chiefly as catabolists. They split particulate antigen into soluble antigenic material and thus prepare it for its catalytic action on the antibody forming cells. The presence of two types of phagocytes is conditioned by the variety of enzyme systems that are needed to digest the various antigens. The granulocytes carry mainly protein and carbohydrate splitting enzymes, while the macrophages are equipped especially for the digestion of fats.

#### EOSINOPHILES AND BASOPHILES

In certain inflammations or at certain stages of inflammation eosinophile and basophile granulocytes may assume prominence. The *eosinophiles* are abundant especially in allergic inflammations which are benefited by antihistaminic drugs. It has been pointed out by Code (10) that in the circulating blood histamine is contained in the leukocyte layer, but that it is absent in the neutrophiles and lymphocytes. For these and other reasons it has been suggested that the eosinophiles elaborate histamine. Dr. Milton Graub in our laboratory, however, has found no correlation between histamine concentration and the number of eosinophiles in the circulating blood.

The *basophile granulocytes* of the blood and the *mast cells* of the connective tissue appear in greater numbers only during the healing phase of inflammation or in chronic inflammation. Large numbers of mast cells are found in the lymph-edematous tissue of elephantiasis (11). It has been shown recently that the metachromatic granules of mast cells contain heparin, and that the concentration of heparin in the various tissues parallels their mast cell content (12-15). It has further been demonstrated that the increase in mast cells in the diseased tissue of elephantiasis is associated with a marked elevation of its heparin content (11). These observations seem to show that the mast cells are heparinocytes, and that they function in inflammation by delivering anticoagulants to facilitate absorption or to prevent clotting of blood and lymph in the obstructed tissue.

#### PLASMA CELLS AND LYMPHOCYTES

It is common knowledge that in a tissue with chronic inflammation plasma cells and lymphocytes may outnumber all other elements. In acute inflammation, on the other hand, they play their rôle chiefly in the regional lymph node. During the first few days of inflammation the local exudate may extend into the sinuses of the node. This phase has been well studied by Wood (16). The main change however takes place in the lymphoid tissue of the node. There is a rapid increase in the number of lymphoid cells leading to enlargement of the node, and there is an increased output of lymphoid cells through the efferent lymph vessel. In our experiments with sheep erythrocytes and typhoid vaccine (17) the weight of the node rose from an average of 0.1 Gm. to one of 0.2 Gm.

(sheep erythrocytes) and 0.5 Gm. (typhoid vaccine) during the first week; the number of lymphoid cells in the efferent lymph rose from an average of 16,000 per cu mm of lymph to one of 60,000.

It was shown by McMaster and Hudack (18) that the swelling of the lymph node in acute inflammation is associated with antibody formation, and that the antibody that appears in the node is not secondarily concentrated here, but it is formed *de novo*. Subsequently it was demonstrated (9, 17) that, following the injection of sheep erythrocytes, typhoid vaccine or dysentery vaccine, antibody production in the node reached its peak on the 5th and 6th day and then declined rapidly. When the antibody titers in the lymphoid cells of the efferent lymph were compared with those of the supernatant lymph plasma, it was found (19) that on the 5th day the lymphoid cells contained 5 to 7 times as much antibody as the plasma; on the 7th day the ratio had dropped to 2 to 3 (19). Lymphoid cells from minced lymph nodes also contained high concentrations of antibody (20, 21, 22). It was concluded therefore that the lymphoid cells were instrumental in antibody production (19, 23).

As the lymphoid cells in lymph are generally regarded as lymphocytes, and in our experiments 93 to 99% of the cells resembled small lymphocytes, the remainder having the appearance of large lymphocytes, we spoke of lymphocytes. Since the lymphoid cells in lymph nodes consist of plasma cells as well as of lymphocytes, the material of Dougherty, Chase and White must have contained both, lymphocytes and plasma cells. It was in order therefore for them to speak of lymphoid cells.

After these various observations had been published, important European studies carried out during the war became known in this country. It had been noted by Bing and Plum (24), Undritz (25) and others that in humans hyperglobulinemia is mostly associated with a comparable increase in *plasma cells*, the highest globulin levels occurring in plasma cell myeloma. Then Björneboe and Gormsen (26) observed that hyperimmunization of rabbits caused marked proliferation of plasma cells in the spleen and other organs. Recently Fagraeus (27) was able to show that antibody may be formed in tissue cultures of spleens of rabbits previously injected with typhoid bacilli. It was found that the red pulp which contained abundant plasma cells formed larger amounts of antibody than the white pulp consisting of lymph follicles. These observations seem to show that it is the plasma cell rather than the lymphocyte that produces antibody and other globulins.

It is well known that the plasma cells and the lymphocytes arise from plasmoblasts and lymphoblasts containing a large nucleus, a large nucleolus and abundant cytoplasm. The nucleolus and the cytoplasm are rich in ribose nucleic acid (PNA), while the nucleus contains desoxyribose nucleic acid (DNA) as well (28, 29). It is common knowledge that during maturation the nucleolar mass of the immature cell dwindles rapidly, the cytoplasm of the lymphocyte is likewise reduced, whereas the plasma cell retains its PNA containing cytoplasm (28, 29). In the mature lymphocyte one finds only a moderate number of fine PNA granules, whereas in the mature plasma cell the cytoplasm is diffusely loaded with this material. Both the lymphocyte and the plasma cell also con-

tain material staining metachromatic with toluidine blue indicating the presence of carbohydrate.

It has also been shown that the nucleic acids are involved in protein production (28, 29). The formation of DNA is associated with the multiplication of chromosomes, that of PNA with the reproduction of cytoplasm (in the dividing cell) and the formation of secretory products (in the mature cell) (28, 29). The reproductive phase in the life of cells is characterized by the presence of a large PNA containing nucleolus, the secretory phase by relative absence of this structure. It appears therefore, that the PNA of the lymphoblast and plasmoblast is accounted for by their reproductive activity, but that the high concentration of PNA in the cytoplasm of the mature plasma cell can not be explained this way; its presence suggests that this cell elaborates protein.

In order to illuminate this relationship further, Dr. Carolyn Forman, Dr. David Drabkin and I have measured the production of the two nucleic acids in the regional lymph node in inflammation and compared it with the production of antibody here. It was found that following the injection of typhoid vaccine into the foot pad of rabbits, the DNA of the node doubled within 2 days and thereafter continued to rise until the 9th day when the experiment was terminated. On the other hand, the PNA was only slightly increased after 2 days, it was doubled and tripled after 4 and 6 days, and then it dropped again. While the DNA curve paralleled the weight curve of the node, the PNA curve was much like the curve of antibody production already described. When sections of the nodes were stained with methyl green and pyronin or with malachite green and acridine red, it was observed that during the period of PNA and antibody production the cellular reaction was largely plasma cellular in nature. On the other hand, the germinal centers began to appear only on the 6th day, and they attained maximum development long after antibody production had ceased. These results leave little doubt that also in the lymph node antibody production is accomplished by the plasma cell.

Our previous finding of antibody in the lymph cells of the afferent lymph has been taken to suggest that the lymphocyte may likewise form antibody. Against this interpretation stands the fact that lymphatic leukemias are not associated with hyperglobulinemia unless they are complicated by plasma cell infiltration. Moreover, Harris, Rhoads and Stokes (30) were unable to extract significant amounts of antibody from the thymus of immunized animals. It appears, therefore, that some of the lymphoid cells that leave the lymph node through the afferent lymph during acute inflammation are plasma cells. In fact, Dr. Elizabeth Mertens in our laboratory has found that the blood of patients suffering from infectious diseases frequently contains a considerable number of small lymphoid cells resembling plasma cells rather than lymphocytes.

While the enzymes of the plasma cells have not been studied, those of the *lymphocytes* have been investigated repeatedly (4). It has been found that the lymphocyte is rich only in adenosinase, a desaminase which splits adenosine. This enzyme acts best in an acid medium and therefore may operate only after disintegration of the cell. These observations suggest that the lymphocyte is instrumental in the destruction of toxic products of the protein metabolism.



As the lymphocyte produces little cytoplasm, its main product being a nucleus, and as it disintegrates rapidly after it has reached its goal, it may have an important function also in protein synthesis. It is indeed reasonable to assume that split products of the nucleoproteins of this cell are used as building stones for the production of new proteins, the lymphocyte being a carrier of reserve nucleoprotein as suggested by Scandinavian authors (27).

It is concluded therefore that the plasma cells function chiefly as anabolists. They synthesize antibody and other globulins. The functional significance of the lymphocytes, on the other hand, is not yet certain. Their chemical composition and their biological behavior suggests that they detoxify adenosine and deliver building stones for the production of proteins.

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# ACUTE RENAL INSUFFICIENCY FOLLOWING TRANSFUSION\*

## PATHOGENESIS AND TREATMENT

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The recent increase of interest in extracorporeal and extrarenal dialysis has made it necessary to reconsider the entire treatment of acute renal insufficiency. More and more clearly it is being recognized that the "forcing" of fluids and salt tends to cause pulmonary and peripheral edema, and is responsible for numerous fatalities.

It is now firmly established that dialysis by means of an artificial kidney can be of great value in the treatment of acute uremia (1, 2, 41, 42, 49). It should also be recognized that many patients will recover *without* artificial dialysis if the fluid and electrolyte balance are controlled according to modern techniques.

The following case of acute anuria resulting from an incompatible transfusion affords an excellent prototype for the evaluation of the factors involved in the management of acute renal insufficiency.

### CASE REPORT

*History.* (Adm. #566362) B. S., a white woman, 28 years of age, was transferred to this hospital on June 19th for the treatment of acute anuria. Two days previously, she had entered another hospital where an elective caesarean section was performed for the delivery of a normal infant. Following the operation, the patient, whose blood was type O, Rh positive, was accidentally transfused with type A blood. The transfusion was terminated after the administration of 250 cc. of blood because of cyanosis. Because of intraperitoneal hemorrhage, the abdomen was reexplored and hemostasis effected. Another incompatible transfusion of about 500 cc. was given post-operatively, 4 hours after the first transfusion. The patient went into severe shock and bled from the operative wound. One thousand cc. of plasma followed by sixth-molar solution of sodium lactate were administered intravenously. The total urinary output on June 17 was 25 cc. On June 18, the output was 60 cc. of grossly bloody urine. The hemoglobin was 30 per cent (Sahli). The red blood cell count was 1.5 million. Vomiting was severe.

*Examination.* On admission to the Mount Sinai Hospital on June 19, the patient was found to be a well developed, well nourished, markedly edematous, pale, drowsy woman. There was no icterus of the sclerae. The tongue was coated. The cervical veins were not distended. There were occasional rales at both lung bases. The heart was not enlarged. The heart sounds were of good quality. There was a soft systolic murmur at the aortic and pulmonic areas. The ventricular and pulse rates were 130 per minute. The blood pressure was 125 systolic and 60 diastolic. The abdomen was slightly distended. A small amount of serosanguinous discharge emanated from the operative wound. There was 2 plus sacral edema, but no pretibial edema.

*Laboratory data.* The hemoglobin was 4.4 Gm. per 100 cc. of blood. The red cell count was 1.25 million. The white cell count was 6,900, of which 47 per cent were segmented forms, 41 per cent non-segmented, 10 per cent lymphocytes and 2 per cent monocytes. There were 45,000 platelets per cu. mm. The reticulocyte count was 1.8 per cent. Bleed-

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ing time was 2.5 minutes, clotting time 6.0 minutes, with good clot retraction in less than one hour. The tourniquet test was negative. The blood prothrombin level was 100 per cent. Spectroscopic examination of the plasma showed the presence of methemalbumin.

The urine on the first hospital day had the color of port wine. The pH was 5.0 and the specific gravity 1.010. There was 2 plus albumin. Microscopic examination of the urinary sediment revealed many clumped white blood cells and a few pigment casts. Table I contains the results of subsequent urinalyses and chemical examinations of the blood.

A roentgenogram of the chest on June 20 showed "unusual clouding of the mesial portion of each lung field near the roots of the lower lobes. The appearance corresponds to so-called azotemic pneumonia, but probably represents a deep pulmonary edema and atelectasis."

*Course.* The patient's course, from the standpoint of changes in the blood and urine and the daily fluid and electrolyte balance, is summarized in Tables I and II, and Chart 1.

The artificial kidney, which requires the use of heparin as an anti-coagulant, could not be employed as a therapeutic measure in this case, because of the recent operation and the post-operative bleeding.

The patient was treated by a medical regime which included strict limitation of total fluid and electrolyte intake, correction of the anemia with small transfusions of whole blood, and correction of hypochloremia with small volumes of 5 per cent saline solution intravenously. A high carbohydrate, high fat, and low protein diet, supplemented by parenteral vitamins, was administered. Penicillin, 50,000 units every three hours, was given intramuscularly because of the development of signs of consolidation over the right lower lobe of the lung.

On this regime, the patient improved slightly, although the temperature remained elevated at 101.6 F. and cough was troublesome. On the 6th day post-operatively, the urinary output was 180 cc. The urine, which had been grossly bloody, then port wine in color, was now clearer and yellow. Sweetened fluids and cereals were retained in large measure. The hemoglobin had been built up by transfusions to 10.4 Gm. from the admission level of 4.4 Gm. Pitting edema of the extremities was much less than on admission, although the patient's face was markedly swollen.

On the eighth day post-operatively, the urinary output had increased to 520 cc. At this time, incipient evisceration at the upper pole of the abdominal wound was treated conservatively with tight binders. The blood pressure had risen to 140 systolic and 80 diastolic.

On the ninth post-operative day, the patient developed symptoms and signs suggestive of multiple small pulmonary emboli. After 500 cc. of blood had been given over a period of five hours, pulmonary edema developed. This complication was treated successfully with oxygen under positive pressure, phlebotomy, intravenous strophanthin, morphine, aminophyllin, and the application of tourniquets to the extremities. Six hours later, there was a recurrence of pulmonary edema which again responded quickly to treatment. The two attacks of pulmonary edema did not delay the onset of diuresis, which occurred on the ninth day. The blood urea nitrogen, however, continued to rise for two more days before beginning its gradual fall to normal levels.

During the period of diuresis, the maintenance of salt and water equilibrium was a problem. The hot weather and sweating added to the difficulty. Normal saline was administered by elysis daily. Despite this treatment, the blood chlorides at first were low, and the patient was drowsy, anorexic, and vomited to the point of acidosis and clinical dehydration. Upon continued treatment with salt, water, and sodium bicarbonate, the blood chlorides and carbon dioxide combining power reached normal levels. The subsequent course was uneventful.

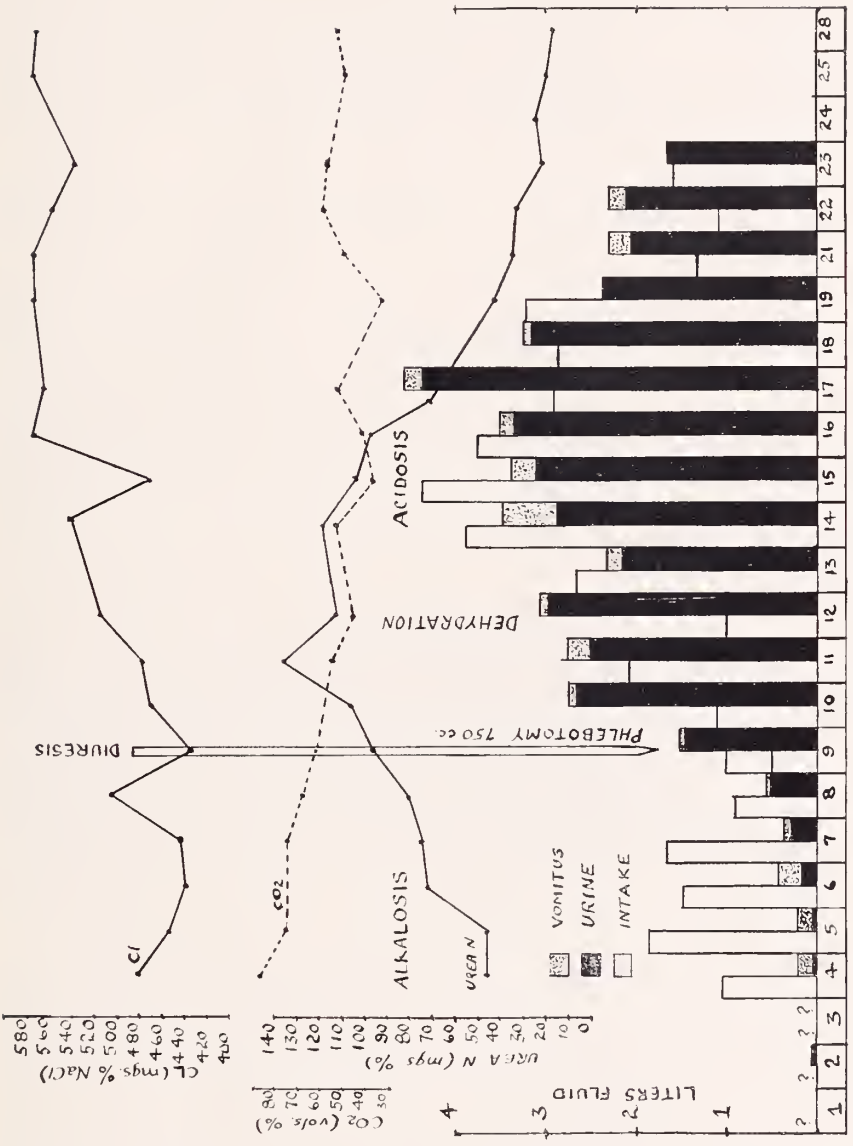
Daily urine specimens showed a specific gravity never above 1.012 during the entire hospital stay of five weeks. Dilution to 1.004 was observed on the thirtieth day of illness. Upon discharge, five weeks after the onset of anuria, with an apparent clinical cure, the blood urea nitrogen was 19 mg. per cent, the phenolsulfonphthalein excretion 40 per cent in two hours (normal 60-85 per cent), and the maximum concentration of the urine to a specific gravity of 1.012 after a seventeen hour thirst.

TABLE I  
*Laboratory data*

OLIGURIA										DIURESIS AND CONVALESCENCE																			
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	21	22	23	24	25	28	29	30	33	37	
Day of Illness.....																													
Urine																													
Volume (cc/24 hrs.).....			25	60	—	68	60	180	270	520	1490	2665	2500	2965	2150	2870	3110	3340	4390	3120	2375	2050	2100	1650					
Reaction.....							AC	AC	AC	AC	AC	AC	AC	ALK	ALK	AC	AC			ALK			AC		AC	AC	ALK	AC	
Specific Gravity							1010	1010	1012	1010	1010	1010	1008	1008	1008	1010				1006			1008		1008	1004	1005	1008	
Albumin.....							2+	2+	3+	4+		2+	2+	2+	1+	tr.				tr.			tr.		f.tr.	f.tr.	f.tr.	f.tr.	
Blood Chemistry																													
(mg.%)																													
Urea N.....							45	45	73	74	80	96	105	136	112	119	103	97	71	42	35	33		21	24	20	17	20	19
Uric Acid.....							7.8	9.8		10.2	10.8	10.5	15.0	16.1	12.0	10.5	8.7	7.0	6.4		5.0								
Creatinine.....							8.4	9.1		11.9	12.4	13.3	13.8	14.3	14.1	10.9	7.6	6.4	5.2			2.6							
Chloride (NaCl).....							480	451	439	441	503	433	468	478	515	538	468	573	562	573	573	558	539	575	573	573	573	573	573
Calcium.....							8.0	7.2																					
Phosphorus.....							4.2	2.7																					
CO <sub>2</sub> (Vol.%).....							86	75		74	68	61		54	45	53	36	40	51		32	49	58	56	48	51	54		
Icterus Index.....							3	3			4	3																	
Total Protein																													
(Gm.%).....							5.2			6.7	5.6	5.8			7.4		8.9	8.1	6.9		7.3					7.4			
Blood																													
Hemoglobin																													
(Gm.%).....							4.4	7.0	8.5	10.4	10.6	14.0	12.2	13.8			12.5												
White Cells (per cu. mm.).....							6900	9450		11350		14400	16200	12100			11000												
Platelets (per cu. mm.).....							45000																						







*Second admission and follow-up.* The patient was readmitted on August 20th for surgical treatment of cholecystitis and cholelithiasis. A cholecystectomy was performed with an uneventful recovery. The average blood pressure was 104 systolic and 60 diastolic.

At this time, two months after the onset of anuria, the urinary output was normal. The hemoglobin was 12.7 Gm. and the red cell count 3.76 million. A faint trace of albumin was found in the urine, and microscopic examination showed 2-3 white blood cells. Maximum concentration was to a specific gravity of 1.020, and the phenolsulfonphthalein excretion was 70 per cent in 2 hours. The blood urea nitrogen was 14.0, the uric acid 3.0, the serum chloride 591 (as sodium chloride), the serum cholesterol 233 (in mg. per 100 cc. of blood). The total serum protein was 6.6 Gm. per 100 cc. of blood.

*Comment.* There are two distinct etiological factors present in this case of acute anuria due to hemoglobinuric, or lower nephron nephrosis (3): 1. Post-operative hemorrhage and shock, and 2. an incompatible blood transfusion of about 750 cc., again followed by shock.

The immediate treatment of shock before admission to our hospital consisted of 1,000 cc. of plasma and an unknown amount of intravenous sixth-molar solution of sodium lactate. On the 4th day post-operatively, because of excessive administration of fluid, particularly sixth-molar solution of sodium lactate, the patient was markedly edematous. Alkalosis was present, as evidenced by a carbon dioxide combining power of 86 volumes per cent. Vomiting contributed to the alkalosis and the hypochloremia (fig. 1). A tourniquet test resulted in carpal spasm. The serum calcium was 8.0 mg. per 100 cc. and spontaneous twitchings were prominent.

There is evidence that alkalosis causes tubular damage and that excessive alkalization may be detrimental to the ultimate recovery of renal function. (3, 4, 5, 6, 7). The effect of hypochloremia *per se* on renal function is difficult to evaluate because it is so often associated with a sodium deficit, acidosis, and dehydration. In this case, hypochloremia and alkalosis were in all likelihood associated with an increased blood volume. Therapy during the period of oliguria and anuria (pre-diuretic phase) consisted of strict limitation of total fluid and electrolyte intake. Small volumes of hypertonic saline were administered in this case only because of the chloride loss in the copious vomitus. Intravenous administration was cautious and slow in order to avoid acute heart failure. Daily transfusions had to be given to correct the severe anemia.

The insensible fluid loss of 500 to 1000 cc. daily has not been included in the tabulation of fluid balance because of the difficulty in its determination. The patient, who was severely ill and threatened evisceration, could not be weighed. When this factor in total fluid output is considered, it will be seen that the restriction of fluid intake in this case was stringent. Despite fluid restriction, the blood pressure rose from 120 systolic and 80 diastolic on the fourth post-operative day, to 140 systolic and 80 diastolic on the eighth post-operative day. Although pulmonary embolization might have been a factor in the pulmonary edema on the ninth post-operative day, the necessary administration of 500 cc. of whole blood was considered to be a precipitating factor.

The elevation of blood pressure and the pulmonary edema following a slow transfusion are dependent on an increased blood volume, which is usually found

in cases of acute renal insufficiency. According to Mason and Zintel (9), in starvation and in disease where food intake is impossible, 300–500 cc. of fluid is produced daily as endogenous water of oxidation from substances catabolized for energy requirements. The liberation of this endogenous intracellular water as a result of tissue catabolism has been suggested to explain the occurrence of increased blood volume and edema despite strict restriction of fluid intake (8).

An interesting observation in the pre-diuretic phase was the secretion of an acid urine in the presence of alkalosis. This difficulty in alkalinization of urine in the oliguric phase has been noted by Burnett and his group (10, 11). Persistent efforts to accomplish this, lead to severe alkalosis and its detrimental effect on the kidneys.

During the period of diuresis and convalescence, the important therapeutic problem was adequate food, salt, and water intake. Management was particularly difficult because of the heat and humidity of the environment. It can be seen from Table II that chloride was unselectively excreted in the urine in fairly large quantity despite the presence of hypochloremia. The danger of hypochloremia, dehydration, and acidosis with symptoms of drowsiness, anorexia, and vomiting is illustrated by this patient, whose intake fell to 1003 cc. on the twelfth day in the presence of a urinary output of 3,050 cc. Careful therapy with sodium chloride, sodium bicarbonate, and water finally led to the reestablishment of a normal blood electrolyte pattern and normal acid-base balance, despite poor tubular function.

#### DISCUSSION

Hemoglobinuric nephrosis with resultant anuria has been ascribed to a combination of some degree of shock and hemoglobinemia, due to sudden intravascular hemolysis. The illness or trauma for which transfusion is indicated in itself may include physiological disturbances which are etiologically significant. Thus, post-operative shock and hemorrhage (as in our patient), anemia, dehydration, and acidosis may be present at the time the transfusion is given, and may predispose to the development of acute renal insufficiency, in the event of a hemolytic reaction.

#### *Pathogenesis*

1. *Shock.* Shock is an important factor in the pathogenesis of the renal lesions which lead to acute oliguria and anuria (16). Trauma, an extensive surgical procedure, or hemorrhage may be present singly or in combination. Circulatory collapse in burns, infections, hyperthermia, and at high altitudes may also lead to acute renal insufficiency with oliguria or anuria.

Pigment casts have been found in the distal tubules even when no hemolytic drug or incompatible blood transfusion could possibly have been the source of pigment (17). The destruction of body tissue or red blood cells must therefore be a factor in the production of these pigment casts. This has been shown to occur in the crush syndrome (17), in burns (18, 19), and in hyperthermia (20).

The effects of inadequate circulation upon the kidney have been studied in relation to shock. When the total circulating volume decreases to approximately



half the normal value, the flow through the kidney decreases to one-tenth, one-twentieth, or even less (21). When this renal ischemia occurs, oliguria or anuria ensues. Van Slyke and his associates (22) divide the effects of ischemia into three stages, depending on its duration: 1. reduced kidney function without damage to nephrons; 2. reversible damage to the nephrons; 3. irreversible damage, with subsequent death from uremia.

Anatomical changes in the kidneys due to ischemia and anoxia have been produced experimentally in rabbits and rats by clamping the renal artery for more than an hour (23, 24).

Corcoran and Page (25) have shown that successive periods of prolonged hypotension and early shock due to bleeding result in progressive renal vasoconstriction, to such an extent that restoration of arterial pressure and blood volume to normal by transfusion fails to restore renal blood flow to more than 50 per cent of normal. After application of partially occluding tourniquets to the limbs of dogs, they showed that within a few minutes renal blood flow was reduced to 50 per cent of normal, and at the end of an hour to about 20 per cent of normal. Renal denervation, prevention of hemoconcentration, and transfusion with restoration of arterial pressure and blood volume were measures which restored only a fraction of the normal renal blood flow. A vasoconstrictor substance was found to be present in the plasma with the onset of renal ischemia. Corcoran and Page believe that the renal vasoconstriction and ischemia is of humoral origin. In human shock, the degree of renal vasoconstriction exceeds that of the rest of the arterial tree.

Most recently, Trueta (26) and his group have demonstrated, in tourniquet shock and by appropriate nerve stimulation, constriction of the renal artery, and a change in the pattern of renal blood flow by which the renal cortex becomes ischemic, the blood stream being diverted into the medulla. Under such conditions the flow of urine in the ureter decreased or was entirely suppressed.

2. *The role of heme pigments.* As was pointed out by Yuile (27), hemoglobin behaves like a threshold substance. It passes through the glomerulus and is reabsorbed by the tubules. If the threshold is exceeded, it then appears in the urine. Intravenous injection of stroma-free hemoglobin solutions have no systemic pharmacologic activity other than a transient renal vasoconstriction. The mechanism of excretion of myoglobin is similar to that of hemoglobin, only its rate of clearance, because of its smaller molecular weight, is 25 times as rapid as that of hemoglobin.

It would seem that the excretion of hemoglobin in itself has no deleterious effect on renal function. Paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, and march hemoglobinuria are examples of hemoglobin excretion without renal damage. De Navasquez (28) demonstrated, in a patient with paroxysmal cold hemoglobinuria, that despite an acid and concentrated urine, there was no diminution in renal function. These observations tend to refute the early explanation of Baker and Dodds (29), who considered the precipitation of hematin casts in an acid urine, with intra-renal tubular obstruction, as the important factors in the renal failure of hemoglobinuric nephrosis.

Bing (30) injected solutions of pure crystalline hemoglobin, myoglobin, and methemoglobin into normal and acidotic dogs. Injection of hemoglobin and myoglobin, even in the presence of acidosis, produced no diminution of renal function and no renal lesions microscopically. Methemoglobin produced no changes in normal dogs, but in all the animals that were acidotic, methemoglobinemia and methemoglobinuria produced a marked decrease in renal function. Pigmented casts, however, were found in the tubular lumens only in those acidotic animals receiving repeated infusions of methemoglobin, after renal failure had already been initiated by the initial injections.

Ross (31) and Foy (32), in reviewing the above work, reached the conclusion that in normal persons, hemoglobinemia and the excretion of moderate amounts of hemoglobin are without ill effects regardless of the reaction of the urine. Renal damage secondary to intravascular hemolysis in humans is ascribed to shock, and prolonged marked reduction of blood flow through the kidney. The presence of pigment in the plasma may contribute to the decrease in renal blood flow by vasoconstriction, and in cases of acidosis, the formation of methemoglobin in the acid glomerular filtrate may aggravate existing tubular damage.

Yuile (33) and his associates demonstrated that hemoglobin precipitation in the renal tubules of rabbits is facilitated by previous moderate tubular injury, whether by a short period of renal ischemia, or by the administration of a chemical poison (sodium tartrate). Under these conditions, casts were precipitated either with an acid or an alkaline urine, but were more numerous with an acid urine.

According to Corcoran and Page (25) renal injury and pigment retention seem to depend on the coincidence of aciduria with oliguria. They observed no change in renal blood flow after the injection of sterile solutions of hemoglobin and myoglobin, or after intravascular hemolysis. They believe the mechanism of renal insufficiency to consist largely of tubular obstruction by pigment casts. The cytotoxic effect of hematin, which is liberated by enzymes from methemoglobin and metmyoglobin, is also considered a possible factor.

Harrison (34) and his associates, in a recent study of the pathogenesis of hemoglobinuric nephrosis in dogs, showed that a high concentration of pigment in the plasma was essential for the production of kidney damage. Although acidosis did have some effect in increasing kidney damage, oliguria was a more important factor. A high concentration of pigment in a concentrated oliguric urine resulted in the precipitation of gel-like casts of methemoglobin. These casts were teased out by microdissection and were shown to be methemoglobin and not insoluble hematin as postulated by earlier workers. The early oliguria or anuria was attributed to tubular obstruction. The subsequent renal damage which followed was attributed to the toxic effect of methemoglobin on the tubular epithelium. Renal blood flow measured directly from the renal vein was normal. This latter finding does not rule out intrarenal vasoconstriction and cortical ischemia as described by Trueta (26).

Flink (15), as a result of his studies, felt that the most important factor leading to the development of renal damage was the plasma hemoglobin concentra-

tion. Dogs with an alkaline urine suffered renal damage approximately as severe as those with an acid urine.

In summary, it would seem from the evidence in the literature that obstruction by pigment casts, and the nephrotoxic effect of methemoglobin are the most probable mechanisms for the experimental renal insufficiency caused by pigment excretion in animals. The renal blood flow does not seem to be altered by free hemoglobin in the plasma, but the possibility of cortical ischemia due to intrarenal arterial vasoconstriction is not excluded. Acidosis may play a part in aggravating the renal insufficiency, but there is inconclusive evidence for it being a prominent primary factor. Oliguria and the plasma concentration of hemoglobin, on the other hand, are very important factors in favoring the precipitation of pigment casts. Methemoglobin—not hematin—has been identified in the pigment casts of the distal tubules. In humans, however, the role of pigment precipitation is in all likelihood secondary. The profound changes associated with inadequate renal circulation are of primary importance (31, 32).

3. *Contributing factors.* Nephrotoxic substances (3) liberated from damaged tissues or red blood cells may affect tubular cells directly, or may cause renal vasoconstriction with tissue anoxia and necrosis.

The physical-chemical imbalance (3, 7) of body fluids may be of importance in initiating or in aggravating renal insufficiency. At the onset of the conditions associated with "lower nephron nephrosis," there may be acidosis due to the liberation into the blood of phosphate and lactate. Intracellular potassium released from injured tissue cells or red blood cells may be a toxic factor (3, 7).

Acidosis, as shown in experimental hemoglobinuric nephrosis, may add to the severity of the renal lesion, even though in itself it might not be a primary etiological factor.

Alkalosis (3, 4, 7) has been shown to cause tubular damage similar to that occurring in the crush syndrome or hemoglobinuric nephrosis, excepting for the absence of pigment casts.

The loss of electrolyte and water by excessive loss of gastrointestinal secretions, or by excessive diuresis, leads to dehydration with lowered plasma volume, hemoconcentration, and nitrogen retention. Whether a loss of electrolyte in itself, apart from the associated dehydration, is a specific nephrotoxic factor, has not been determined. Hypochloremia and hyponatremia are often associated with renal insufficiency (6, 7). It is difficult, however, to separate the effect of low electrolyte concentration from that of dehydration, reduced blood volume, and the concomitant renal circulatory changes (35).

Hypochloremia may be induced in animals without evidence of renal damage if plasma volume and osmotic pressure are sustained (36). The interrelation between the sodium ion, the volume, the hydrogen ion concentration, and the osmotic pressure of the body fluids is such that it is difficult to isolate the sole effect of a low blood sodium on renal function.

4. *Mechanism of oliguria and anuria.* Five principal mechanisms have been suggested for the explanation of the oliguria and anuria which are seen in lower nephron nephrosis. 1. The disturbance of renal circulation, with hemodynamic

changes which lead to a decrease in filtration, is probably the most important early factor. This includes the Trueta (26) mechanism. 2. Tubular obstruction, by casts or cellular detritus (37), is another factor. Recent work by Harrison et al. (34) in experimental hemoglobinuric nephrosis supports this view. 3. Dunn and his associates believe that the oliguria is due chiefly to back leakage of glomerular filtrate through the damaged tubular walls (53). 4. Peters (38) has stressed the increase in intrarenal pressure with its effect in reducing effective filtration pressure. 5. The action of an antidiuretic hormone, presumably from the posterior pituitary, has been suggested by Brun and his associates (39).

### *Pathology*

The kidney lesions which are produced by intravascular hemolysis from whatever cause are those of lower nephron nephrosis. The histopathologic picture has four distinctive features, according to Lucké (3):

1. Degeneration or necrosis which involves selectively the lower segments of the nephrons—the thick limb of Henle's loop and the distal convoluted tubules.

2. Edema and cellular reaction in the stroma around the more severely damaged or disintegrated portions of the tubules. These changes are commonly associated with thrombosis of the adjacent veins.

3. Casts of a heme pigment which lie within lumens of the lower segments and of the collecting tubules.

4. Slight or no change in the glomeruli and proximal tubules. Cells of the proximal tubules are at times slightly swollen and somewhat more granular. Frank degeneration or actual necrosis of the proximal tubules is very rare.

The absence of significant changes in the proximal tubule is in contrast to the severe changes which are seen following mercury intoxication and other renal poisons, which damage this segment almost specifically (12).

According to Ayer and Gauld (13), the earliest changes three hours after hemolysis are glomerular swelling, slight cloudy swelling of the proximal convoluted tubules, with pale acidophilic material in their lumina. Dark red to brown material is seen in the distal convoluted and collecting tubules. By the third day, there is brick red pigment within the cells of the distal convoluted tubules with some necrosis and sloughing of these cells. By the sixth day, there is interstitial edema and leukocytic infiltration around the convoluted tubules, with marked desquamation of the tubular cells.

From the standpoint of therapy, it is important to note that, by the seventh day, mitotic figures appear in some of the tubular cells, indicating regeneration and repair. This is similar to the regeneration and repair seen in other instances of toxic injury to the kidneys.

By the tenth day, there is replacement of completely destroyed tubules by inflammatory cells and fibroblasts, with numerous cellular casts in the distal convoluted and collecting tubules.

Burwell et al. (14) reported the pathological findings in the kidneys of a patient who died of homologous serum hepatitis three months after anuria second-



ary to intravascular hemolysis. The changes were not extensive and were compatible with the healed stage of the pathological sequence described by Ayer and Gauld. Single nephrons or groups of nephrons were found to have been destroyed. Few glomeruli and no blood vessels were involved.

Flink (15) has clearly shown, with his biopsy technique, the progress of hemoglobinuric nephrosis in dogs to the stage of almost complete healing. In one dog, 112 days after injection of hemoglobin, an occasional atrophic tubule and a rare cast were the only evidence of previous hemoglobinuric nephrosis.

### *Treatment*

The clinical course of a hemolytic transfusion reaction with acute renal insufficiency may be divided into three periods: 1. the immediate emergency period of the first twelve hours after hemolysis, 2. the period of oliguria and anuria averaging seven to fourteen days, and 3. the period of diuresis and beginning convalescence of about seven days' duration. The duration of the second and third periods will depend on the severity of the renal lesion.

From the discussion of pathogenesis and pathology, it is evident that the exact nature of the acute anuria which follows acute intravascular hemolysis is unknown. Certainly its clinical occurrence is associated with predisposing etiological factors which have been shown experimentally to cause tubular damage. Shock from a surgical procedure and anaesthesia, acute hemorrhage, prolonged dehydration, and anemia, are such factors. Singly or in combination, they usually precede the acute hemolytic episode of an incompatible blood transfusion.

### *The Immediate Emergency Period*

The "immediate emergency period," following the hemolytic reaction itself, is characterized by shock. The degree of shock will depend in some measure on the severity of the predisposing etiological factors, which are characterized by decreased blood volume and hypotension. Hemorrhage following a transfusion reaction, as in our case, is a frequent complication which contributes to shock. The administration of compatible whole blood and plasma is essential. The quantity of each administered will depend on the extent of hemorrhage and the degree of hypotension and shock. Administration of water and electrolyte should be avoided during this period. It only leads to pulmonary edema and necessitates phlebotomy. The therapy of this immediate period is, therefore, the emergency management of shock with whole blood and plasma.

### *The Period of Anuria and Oliguria*

The second period is the period of anuria and oliguria. Since prolonged shock causes tubular damage, adequate therapy in the first few hours after the reaction will reduce the severity and duration of the anuria and oliguria of the second period. It is during this period that regeneration of tubular epithelium and repair of renal damage occurs. The maximum degeneration of tubular epithelium occurs at about five to seven days (15). Tubular regeneration begins as early as the third or fourth day. The healing process is rapid. Most damaged tubules are relined within ten days (3). Thus one should expect the critical

period for survival at about seven to ten days. This has been found to be the case in the lower nephron nephrosis of the crush syndrome, where the first week is the critical period and where patients surviving to the eighth or ninth day recover (40). Burwell et al., (14) reviewing non-fatal cases collected from the literature, found diuresis to occur in most instances from the seventh to the eleventh day. The great majority of fatalities occurred in the first ten days. In cases of post-traumatic anuria studied by Lucke (3), 86 per cent died within ten days. Thus it would seem that if death does not occur during this critical period of seven to fourteen days of anuria and oliguria, then diuresis and gradual recovery may be expected.

The principal aim of therapy in this period is to prolong the patient's life until tubular regeneration can occur and until diuresis heralds recovery of function. It is during this period that judicious administration of fluid and electrolyte is most important. Death during this period is most often due to overtreatment with fluid and sodium salts in an effort to cause urine output (8). In the presence of oliguria and anuria, fluid retention leads to pulmonary and cerebral edema. In the past few years, we (41, 42, 43, 44) and others (45, 46, 47, 8) have stressed this important principle of fluid and sodium restriction. A total fluid intake of 1000 cc. per day, under usual circumstances of environmental temperature and humidity, is sufficient to maintain hydration, which has already been attained during therapy of the immediate emergency period.

To correct acidosis, alkali should be administered cautiously in a dosage form requiring a minimal fluid intake. Sodium bicarbonate by mouth, or intravenously in a five per cent solution is effective. The use of sixth-molar solution of sodium lactate intravenously necessitates the intake of a large volume of fluid and should be avoided. Hypertonic molar solution of sodium lactate intravenously may be administered slowly. Excessive alkali should not be administered, either in the overzealous correction of acidosis or in the attempt to alkalinize the urine. There is indirect and direct evidence that alkalosis *per se* causes oliguria and renal insufficiency. Alkalinization of the urine may be impossible during this period. Despite alkalemia, the damaged kidneys are unable to excrete an alkaline urine. Since alkalinization of the urine has its dangers and since its effectiveness in hemoglobinuric nephrosis has been questioned (32) this therapeutic measure, which is usually employed, should not be carried too far. Alkali should be cautiously administered only to correct the acidosis.

It has not definitely been established whether hypochloremia in itself dissociated from hyponatremia and dehydration, is deleterious to renal function. Certainly with hypochloremia and an adequate or increased blood volume, the administration of sodium chloride and fluid to correct the hypochloremia might lead to an increased blood volume and acute heart failure. During anuria or oliguria, complete restriction of salt intake would be the rule, unless hypochloremia were associated with copious loss of chloride in the vomitus or diarrheal stool. Under such circumstances sodium chloride replacement might be indicated. It is clear that chemical examination of the blood and urine is necessary to determine the daily requirement of sodium chloride, or sodium bicarbonate.

There may occur a secondary anemia during this second period which is in-

dependent of blood loss and is etiologically related to the acute progressive uremia. If the blood hemoglobin concentration is not too low (below 7-8 Gm. per 100 cc. of blood), transfusion should be deferred until an adequate urine output is present. The possible danger of acute heart failure is thus avoided. However, if anemia is severe, small transfusions (100 to 250 cc.) of red blood cells are indicated.

The hypocalcemia of the acute uremic state, with its associated muscular twitchings, is treated with intravenous calcium gluconate.

Oversedation should be avoided. The cumulative action of a retained fixed sedative and the cerebral effect of uremia may be fatal. Paraldehyde may be used, if hyperexcitability is present.

In the presence of heart failure, digitalis is indicated. Since excretion of the drug is markedly limited, maintenance dosage is to be determined very cautiously.

A very low protein, high carbohydrate, and high fat diet is instituted if vomiting is not too troublesome. If it is, then carbohydrate is administered intravenously in concentrated solution. In this period of acute renal insufficiency of about two weeks, a vitamin deficiency is unlikely to occur. Water soluble vitamins are usually administered, although it is doubtful whether they affect carbohydrate metabolism in the face of a negligible protein intake.

It is clear that the guiding therapeutic principle of this second period of oliguria and anuria is the maintenance of metabolic equilibrium in the face of disturbances in protein catabolism, acid-base, and fluid balance, of the acute uremic state. The aim is to maintain life until the time of diuresis and recovery.

It is during this period that an artificial means of dialysis may serve as a useful therapeutic adjuvant when, despite proper management, the condition of the patient deteriorates. Peritoneal lavage (48) and extra-corporeal dialysis of blood through a cellulose acetate membrane (49) are the most efficient methods available.

#### *The Period of Diuresis and Beginning Convalescence*

The principal aim during this period is to maintain water and electrolyte balance despite copious loss of water during diuresis. Sodium and chloride are usually lost in the urine in large quantities and must be replaced. If not replaced, dehydration and acidosis may result in a very short time.

It is most important to know that there are instances of tubular dysfunction where sodium and chloride are retained in excess of water (50). Under these circumstances administration of sodium chloride would be disastrous, leading to pulmonary and cerebral edema.

It is clear that chemical determinations of chloride in the blood and urine are essential in determining whether sodium chloride is to be administered.

Nausea, vomiting and diarrhea may recur early in this period of diuresis. The exact etiology is obscure. Shifting of intracellular water, recurring acidosis, and dehydration are possible factors. Potassium loss in the urine may also be a factor (51, 52).

With improvement in renal function, the blood constituents gradually return to normal. Appetite returns. A regular diet is tolerated, and fluid intake parallels the urinary output. During the period of convalescence it is essential to employ a high caloric diet in order to restore the weight lost as a result of body protein catabolism during the period of acute uremia.

#### SUMMARY

The successful medical management of a complicated case of acute renal insufficiency following transfusion reaction is recorded in detail in order to illustrate the important clinical and laboratory features of successful therapy.

A review of the relevant literature pertaining to pathogenesis and pathology of hemoglobinuric nephrosis is presented as a background for the discussion of treatment.

Medical management has been divided into the therapy of three clinical phases:

1. The immediate emergency period,
2. the period of anuria and oliguria, and
3. the period of diuresis and beginning convalescence.

The treatment of shock is of prime importance in the first period.

Fluid and salt restriction is imperative during the second period. Whatever the mechanism for the anuria and oliguria may be, it is clear that excessive fluid administration will not initiate urine flow.

The electrolyte and water equilibrium must be carefully controlled during the period of diuresis. It is important to note that sodium may be either lost excessively in the urine, or retained in excess of water during this period.

The use of peritoneal lavage, or an artificial means of extra-corporeal dialysis is considered an adjuvant in therapy during the period of oliguria and anuria. It is, however, not a substitute for correct medical management, which aims to maintain the physiological equilibrium of the patient until recovery of renal function occurs.

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## A PSYCHOLOGICAL STUDY OF NEURODERMATITIS WITH A CASE REPORT\*

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In recent years there has been an increased awareness on the part of physicians of the interplay between the body and mind in the causation and continuation of somatic disease. This is as true of dermatologic conditions as of other disorders. The relation between emotions and such skin manifestations as blushing and sweating is part of common knowledge. The rôle of emotional factors in many dermatologic conditions has been long suspected (1, 2, 3) and of late the psychosomatic factors in urticaria (4), lichen planus (5), atopic dermatitis (6, 7), seborrheic dermatitis (8), psoriasis (8), neurodermatitis (9, 10), chronic lichenoid discoid dermatitis (11), etc. have been discussed in the literature.

The skin, by virtue of its function as both a protective and a sense organ, is bound not only to an integral part of the bodily economy, but plays an important rôle in the psychic activity. As Fenichel (12) has pointed out, the skin has four characteristics that stem from its physiologic function and its location as the external organ of the body, serving as the boundary between the latter and the external world: 1. Its protective function from external stimuli, which may be used by the organism to project disturbing internal psychic stimuli; 2. Its rôle as an erogenous zone, a rôle which has its beginnings in early infancy with the pleasure of warmth and the displeasure of cold as the prototype of later erogenous usage; 3. The skin, by being on the surface and in part visible to others, serves well to satisfy exhibitionistic desires; 4. The skin is a site of anxiety equivalents, for anxiety—as an expression of increased sympathetic activity—is displayed partially through the blood vessels of the skin.

The way in which these characteristics, either singly or in combination, are brought into play will determine the occurrence of a psychogenic dermatitis. What governs the exact form of the dermatitis is not clear, but once a particular type of dermatitis is developed, it in turn may serve as the expression of an emotional conflict in line with the aforementioned four characteristics.

The following case of neurodermatitis is illustrative of these factors and also illustrates an occurrence during therapy that is becoming increasingly common as our work with psychosomatic conditions progresses.

### CASE REPORT

*History.* A woman, aged 38 years, was admitted to the dermatology service with a two and one-half year history of pruritus, "eczema," and scaling of the skin. This started about three months after her youngest child, a boy, developed poliomyelitis with complete

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paralysis, which caused the patient to have "almost a nervous breakdown." After this there developed a dermatitis, which at first was felt as tightness on her head, followed by dryness and scaling of the scalp. In two to four weeks after the onset of symptoms her entire skin was itching, red, dry and scaling. The itching which was more prominent at night, was so intense that she felt she had "to tear myself apart to get relief." As this affliction became generalized she sought medical advice and in the course of the next  $2\frac{1}{2}$  years she saw about twenty physicians. Numerous methods of treatment had been used, including benadryl, pyribenzamine, novocaine, typhoid vaccine, autohemotherapy and intravenous calcium, all without any benefit. During the same period she had been hospitalized twice, again without result. She had been advised to go to a different climate; she was unable to do this. The three months preceding her admission were marked by moderate anorexia.

Fifteen to 16 years previously she had had seasonal attacks of hay fever accompanied by cracking and scaling of the skin in the folds of the antecubital fossae. These attacks occurred seasonally for four years, and then stopped the year after her marriage, thirteen years ago.

*Examination.* There were enlarged suboccipital, axillary and inguinal lymph nodes. Her skin was diffusely reddened, thickened and scaling with severe excoriations on her arms, legs and trunk. There were areas of ulceration on her legs and back with evidence of secondary infection. Her scalp was covered with a thick, white, moist scale. The remainder of the examination was negative.

*Laboratory data.* Blood: hemoglobin, 82 per cent; white blood count, 10,250 with a differential of 62 per cent segmented polymorphonuclear leukocytes, 8 per cent non-segmented polymorphonuclear leukocytes, 22 per cent lymphocytes, 3 per cent monocytes, 4 per cent eosinophils and 1 per cent basophils. Urinalysis and blood Wasserman test were negative. Blood chemical determinations were within normal limits. Blood sedimentation rate was elevated to 55 mm. per hour. Chest x-ray was negative. Because of the state of her skin, intradermal tests were not attempted.

The *diagnostic impression* was neurodermatitis with secondary infection and lymphadenitis. Because of the previous therapeutic failures and the close time relationship between the onset of her dermatitis and the illness of her son, it was felt that psychotherapy should be attempted in addition to local treatment. She was accordingly transferred to the psychiatric service where, besides psychotherapy, she received Burow's emulsion to her skin, potassium permanganate baths and benadryl (250 mg. initially, increased gradually to 350 mg. daily). This local regime was followed, with the exception of benadryl, as long as she stayed on the psychiatric ward. Benadryl was discontinued ten days before she left the hospital.

*Psychiatric investigation* showed that she was the sixth of seven children born to a lower middle class family where there were frequent economic difficulties. Her father, who had asthma and diabetes, she described as a selfish and temperamental man, easily upset by any untoward incident in the home, very strict with all the children and quarreling frequently with the mother. She felt he was really interested in only two things in his life—money and the house that he owned (describing, for example, how he threatened to evict her and her husband from their rooms in his house when they were unable to pay the rent on time). Whenever she talked of him she spoke in a very hostile manner, blaming him for the unhappy childhood she had had. Yet in spite of this apparent hostility, when he died in 1942 she was terribly upset. Her mother was described in glowing terms as a very good woman who had had to put up with a great deal from the father, yet in spite of this managed to raise a family and keep a very clean, neat house (although often not up to the patient's high standards). The mother always took the patient's part during the frequent arguments with the father, usually about money. As a child she apparently did not resent her mother's obvious favoritism toward her sister, five years younger than the patient, but later in life she realized that the mother's attitude was not right and not fair. She felt the same way about her mother's failure to give her any sex education. Her mother's death provoked an "hysterical" outburst.



The patient's relations with her various siblings were probed in some detail. She had always been hostile toward an older sister accounted for on the basis of that sister's close identification with, and resemblance to, the father. The next oldest sibling was her closest confidante; they worked together and one would quit a job if the other left. They slept together, but whether there was any sex play between them was not ascertained.

The patient began to work at the age of thirteen, after graduating from grammar school. She had been a good student, and although she wanted to continue her education her father insisted that she go to work to help the family financially. For the next twelve years she contributed money to the family until her marriage to a man she had known for six months. She had received no sex instruction at home and had been frightened by the onset of menstruation. She thought it "meant becoming a lady" and did not feel prepared for that. She denied masturbation. She started to go out with boys at the age of seventeen, but allowed no sex play other than occasional kissing prior to her marriage. This union was opposed by her family, since they did not feel he was "good enough" for her. She described her marriage as successful in all respects, although for the first few years they were beset by money difficulties; at present, however, they were comfortable financially. Her husband is easygoing, understanding and placid, so that she assumed the dominant role and wished "he was more of a man." Their sexual relations were described as satisfactory; there was adequate fore-play and both of them reached orgasm. They wanted a child and their first, a boy, was born twelve years ago. Their second child, also a boy, is eight years old and was unwanted. Since the birth of the younger son she had always been greatly concerned about his health and safety; she often took his temperature rectally and limited his activities in fear of possible illness or accident. When he first became ill with poliomyelitis she insisted on treating him at home but after three days he became totally paralyzed and only then did she permit hospitalization. Since then he has remained paralyzed, living a vegetative existence in an institution where she has visited him faithfully. Her dermatitis started three months after the onset of her son's illness and just after he had definitely passed the critical stage. Ever since the boy's paralysis started, the patient's husband has accused her of responsibility for the hopeless outlook because of her error in judgment in not allowing him to be hospitalized immediately. All during the early interviews with her, she cried whenever she spoke of her son, attributing this to her feelings about the hopeless condition of her paralyzed boy.

As the psychiatric investigation progressed her hostility to her father became more obvious and was expressed repeatedly. In addition, she showed considerable hostility toward her husband. For example, after working 14 to 16 hours in his grocery store he was forced to rub her skin with various ointments, because it was "too messy" for her to do. (That she got erotic gratification from this seemed evident, but was not clearly brought out.)

She said that she had always been proud of her fine skin and would often examine herself carefully in the mirror. She had always blushed without much provocation and had always perspired profusely until the onset of her dermatitis. She blushed frequently during interviews, particularly when sexual topics or her son's illness were discussed. She always dressed well, but she said she did this for her own pleasure rather than for its effect on others.

It was learned that the patient had been extremely obese from her early childhood until the age of 16. She said she first became aware of it at the age of 14 when her friends ridiculed her because of her prominent breasts. Only after quarreling with her mother for the next six months did she get permission to wear a brassiere. At 16 she put herself on a rigid diet, but shortly thereafter she broke the restrictions and remained obese. Nothing more of the oral drives of the patient was learned, but it was noted that she expressed herself in every ward situation in a flood of words delivered in a hostile, aggressive manner. While on the ward she also acquainted herself with every patient's problems and attempted to treat them.

All of her life she had been an extremely neat, fastidious person who had an overwhelming urge to complete things without regard for how much this might interfere with other re-

sponsibilities. A very marked concern about money was evident. She claimed that she tried in every way to be unselfish toward others, not wanting to take after her father in any way, even though in her own household she re-enacted her father's role in dealing with her husband.

*Course.* Twelve days after admission to the psychiatric service the patient's pruritus was still intense and she still felt as though she could "tear myself to pieces." During the day she was able to control this, so that the excoriated areas were beginning to heal. Her skin, however, was still edematous, red and scaling.

In an attempt to control the pruritus by suggestion, she was hypnotized on the twelfth day after her transfer to the psychiatric service. While in a state of light somnolence, with only the usual hypnotic suggestions being given to increase the depth of hypnosis, she suddenly began to cry and sob, stating vehemently how badly and how guilty she felt about the illness of her son. She then stated spontaneously, "I blame myself for having kept him at home. I feel guilty for his illness and my skin has shown my guilt." She was asked about the pruritus and replied "this is the itching of my conscience which bothers me because of my little boy." She continued to sob and cry bitterly, but further attempts at mental catharsis or at obtaining new information were unsuccessful. She was accordingly awakened with the suggestion that the itch would be gone from her right arm. A few hours later it was noted that the lobster red color of her skin had become much lighter. Three days later she told her therapist that she didn't know why, but starting late in the afternoon following the hypnosis (although at first she did not realize this time relationship) her skin had started to clear markedly and when she wiped her face the scales fell off in great profusion. This had also begun to occur on the rest of her body. The pruritus was less intense except on her right arm. During the weeks following her emotional reaction under hypnosis her skin continued to clear with a gradual disappearance of the edema, redness and scaling and almost complete relief from the itching.

In the subsequent therapeutic interviews she at first rejected the suggested connection between the experience under hypnosis and the improvement in her skin, saying she had earlier expressed her feelings about her boy's continued illness without relieving the dermatitis. It was pointed out to her that there were two differences, first, the expressed emotion which had not been displayed before and also her feelings about the role she played in the first three days of the son's illness contrasted with those during the last two and one-half years of paralysis. It was explained that she had felt responsible for, and, hence, guilty about, the extent of his condition, and since she was the sort of person who had always reacted to emotional situations with her skin (blushing, perspiring), this outlet for her guilt was used. When she apparently felt a need for punishment to expiate her guilt, the pruritus had served that purpose. Her own words (under hypnosis) were recalled to her to reinforce this suggestion. She came to accept this explanation. About a week after the first hypnosis, she was again hypnotized, but other than denying she was selfish like her father (as her husband claimed), no new information was obtained.

Two weeks after the initial hypnosis, she began to express fears that her child had died, but on being reassured, accepted that he was still alive. That night she was unable to sleep because "I have something terrible to tell the doctor." The next morning she told of indulging in mutual masturbation with her husband since her child's illness, but before her dermatitis started. She said she knew it was wrong and felt guilty about doing it, but it was the most satisfactory sexual relationship they had had. She compared the feeling she got when scratching herself to that she felt when her husband caressed her during their mutual masturbatory experiences. She was very agitated while telling this and no deeper probing was done.

For the next ten days she expressed many delusions about her child and husband, was agitated and disturbed, had occasional hallucinations and became incontinent of urine and feces. The Rorschach test reinforced the clinical impression of acute schizophrenia and when she became too disturbed to handle here she was transferred to a psychiatric hospital. During this psychotic period her skin continued to improve.

*Follow-up.* The patient was at a state hospital for three months, receiving electroshock treatments, resulting in a remission of her mental symptoms. At the time of discharge from the mental hospital her skin was completely clear except for a patch of scaling on the dorsum of each foot. When last seen (February 4, 1948) her skin was still clear, she had resumed family obligations and was able to accept her son's complete incapacity. She had gained 39 pounds and was quite obese.

#### DISCUSSION

This case presents several noteworthy features in spite of the many gaps in our knowledge of her genetic development. There is sufficient evidence, however, to suggest a connection between the dermatitis and the specific emotional conflict situation, and the utilization of the illness to her own advantage.

The immediate precipitating cause of her dermatitis was the illness of her son and, more particularly, her conduct in the boy's illness. From that point of view, the first three days of the disease were the crucial ones, for in keeping him at home she was apparently acting out her hostility to him. This existence of hostility is to be found in the fact that he was an unwanted child and further revealed by the overconcern for his health and safety she displayed until the onset of the poliomyelitis. Her stress on checking his temperature rectally and her limitation of his activities suggests a reaction-formation against hostility. Once this hostility was acted out in the three days prior to his hospitalization—which would be the time when a truly concerned mother would have followed the advice of her physician—she developed tremendous guilt feelings, constantly reinforced by seeing in her invalid boy the result of her hostile act toward him. This guilt was further reinforced by her husband, who often accused her of causing the boy's subsequent invalidism. If such guilt was present, however, why was it not expressed immediately?

The clue to that would seem to lie in her particular type of obsessive-compulsive character, with its meticulousity and especially its dissociation between the emotion and its cause. Thus, she was able to recall consciously her omission regarding her child, but it was not until the affect, or emotion, associated with this event was expressed openly and made conscious that any therapeutic progress was made. Another feature of the pre- and post-hypnotic therapy was a shift in emphasis from the two and one-half years of illness to the three days preceding hospitalization. This was made possible by the emotional catharsis under hypnosis.

Once the feelings of guilt had appeared after the boy's illness and had been dissociated (and repressed) from conscious thought, the emotion, being strong, sought an outlet. This outlet was apparently the dermatitis. In discussing the mechanism of the production of the dermatitis the following was suggested by one of us (S. P.) in a note on her chart:

"The patient's dermatitis from our first observations of the case could be described as a generalized rather dusky erythema with superimposed desquamation. Quite characteristic were the scattered, fairly circumscribed areas of lichenification which were situated in those areas of the body readily accessible to scratching and rubbing. There was an intense pruritus.

"The first sign of improvement was the gradual disappearance of the itching which was accompanied by a disappearance of the edema. Following this there was a gradual disappearance of the desquamation and lichenification. Symptomatically, accompanying the above skin changes, there was a marked lessening of the pruritus.

"The mechanism of the causes of her dermatitis, as I see it, is as follows:

"With her guilt complex, there was continuous blushing of the skin. This resulted in chronic small vessel dilatation with pruritus. Rubbing and scratching such a skin resulted in an increased transudate and even an exudate through the dilated capillaries. This gave us the edema. The epidermis over this inflamed skin responded with desquamation. Chronic lichenification followed the long continued scratching of such an inflamed epidermis."

If such was the mechanism, why was it through the skin that this conflict was expressed? There are indications from her history that there was a certain fixation on the skin from her early life onward. She had always blushed on the slightest provocation. She had been proud of her fine skin and showed many exhibitionistic tendencies. Her obesity may in part have been related to this. At any rate, it was through her skin that she had previously worked out her exhibitionistic desires. It would, therefore, be through her skin that she would display her guilt to the world. Possibly this was mediated through some physiological mechanism such as described above.

Since the dermatitis apparently served as an outlet for the profound feelings of guilt, it had a very important function in her psychic economy. Once the guilt became conscious the dermatitis no longer served as an outlet, and she was left without the means of handling this extreme amount of emotion. The effect was for the patient to regress into unreality in an attempt to deny these feelings and project them onto the outside world. This type of mechanism for dealing with unpleasant emotions is typical of schizophrenic thinking. The result of these projections was the distortion of the patient's personality and the loss of contact with reality which are characteristic of a psychosis. The various paranoid ideas which developed during the course of her psychosis are probably accounted for by the marked masculine rôle she played through identification with her father.

Besides serving as an expression of guilt, her dermatitis, once developed, had several advantages. It was used as an expression of hostility toward her husband (the rubbing of her skin with ointment, for example) and at the same time there must have been a certain erotic gratification from these maneuvers. Her statement that the mutual masturbatory experience gave her the same sensation as scratching herself also suggests that the dermatitis was a source of erotic stimulation. (This, of course, may have been secondarily elaborated during her psychotic period to rationalize her scratching.)

An unexplained series of events was the occurrence of her asthma and eczema a few years before her marriage and their subsequent disappearance. The eczema may also have served to sensitize her skin so that the severe conflict later on was expressed through this area.

From a therapeutic point of view, this case illustrates the danger of too rapid



removal of a patient's somatic symptoms when there are neurogenic components involved. For this emotional energy must express itself in a way which is both effective as an outlet as well as acceptable to the patient's ego. The dermatitis fulfilled both needs. Once the guilt became conscious, it was not acceptable to the ego and had to be projected outward. If, however, through more prolonged therapy the quantity of affect made conscious at any one time was not so great, it could have been handled without disturbance of the patient's personality.

Since many of the patients on the psychosomatic ward show a similar psychological pattern, it would appear that, on the basis of this case, therapy of psychosomatic disorders should be approached with caution and with a thorough knowledge of the psychodynamics involved. Or, perhaps, a superficial supportive (anaclitic transference) type of therapy, based on a knowledge of the deeper dynamics, can be done without danger.

#### SUMMARY

A woman with neurodermatitis of two and one-half years' duration is presented. Guilt over her child's illness apparently precipitated the skin disorder. Other psychologic factors in the illness are presented and discussed. During the course of psychotherapy she developed an acute psychotic episode. The implications of this for the therapy of psychosomatic disease are discussed.

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## SARCOSPORIDIOSIS IN TWO CASES WITH TRICHINOSIS\*

HAROLD S. ARAI, M.D.

Sarcosporidiosis is a disease caused by parasites which characteristically invade the musculature. The parasites are called Sarcosporidia and belong to the genus *Sarcocystis*. They were formerly regarded as protozoa but are now believed to be fungi (1, 2). They infest the striated muscle fibers and, rarely, the unstriated muscle fibers and connective tissue of mammals, birds and reptiles. The infestation is quite common among such mammals as sheep, cattle, horses and pigs. Man is rarely affected.

The parasite is found within individual muscle fibers as an elongated body called a *sarcocyst* or *Miescher tube*. Both adult and immature forms occur with considerable morphological variations, depending on the species of the parasite and the host (3, 4). A typical adult sarcocyst has a distinct external membrane which frequently shows radial striations. Arising from the external membrane are septa which divide the cyst into compartments containing numerous spherical, oval or crescentic spores called *Rainey's corpuscles*. The central area is commonly hyaline. The immature form contains numerous spores but it is smaller in size. The external membrane may be indistinct or absent, and is usually without radial striations. The septa and the hyaline central area are rarely demonstrable. Both adult and immature forms have been observed in man, the latter more frequently.

Sarcosporidiosis in man is rare. Up to the present there are only eleven reported cases which have been generally accepted as being authentic. In four of the eleven cases, Sarcosporidia were found in the myocardium. In all cases the disease was an incidental finding on microscopic examination of the tissues, for in man the parasites are not grossly visible and their infestation does not cause death.

Kartulis (5) in 1893 described the parasites in the skeletal muscles of a Sudanese who died with multiple abscesses of the liver and abdominal muscles. This report is generally accepted as being the first authentic case in man. Baraban and Saint-Remy (6) in 1894 found sarcocysts in the laryngeal muscles of an executed man. This was followed by two cases of Darling (7) who in 1909 reported the presence of sarcocysts in a biopsy specimen obtained from the biceps muscle of a young negro suffering from typhoid fever. A repeat biopsy was done in the same patient four months later and the parasites were no longer demonstrable. His second case was an East Indian known to have had malaria and hookworm disease and who died with an obscure fever, probably malarial in origin. The sarcocysts were discovered in the lingual muscle (8). Manifold (9) in 1924 described the first authentic case of such myocardial infestation in man. The sarcocysts were found on microscopic examination of the myocardial sections; no mention is made as to the other diseases which the man undoubtedly had. Lambert (10) in 1927 observed the parasites in the myocardium of a

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negress who died with bronchopneumonia and acute rheumatic heart disease. Vasudevan (11) in 1927 noted sarcocysts in the pectoral muscles of a man with abscess of the chest wall. A similar case was reported by Naidu (12) in 1928. Bonne and Soewandi (13) in 1930 discovered the parasites within a cavernous hemangioma of the lip. The third authentic case of myocardial involvement was published by Hewitt (14) in 1933. Clinical details of this case are not available. The fourth undoubted case of Sarcosporidia in the myocardium was reported by Gilmore, Kean and Posey (15). They found the organisms in the myocardium of an 11-year-old girl who probably died of malaria.

The following is a report of two cases of sarcosporidiosis of the myocardium which were incidental findings in patients who died of acute, severe trichinosis.

#### CASE REPORTS

*Case 1. History.* (Adm. #418573, P.M. #10648). The patient was a white man, aged 31 years, a salesman by occupation, a native of Germany, who had come to this country several years ago. He was in good health until the onset of his fatal illness. Three weeks before admission he and three others had eaten ham purchased at a neighborhood grocery store. A week later he was seized with epigastric distress and vomiting. On the same day, profuse diarrhea began which lasted for four days. About this time he developed aching pains over both trapezius muscles and forearms, a fever ranging from 100° to 103°F. and marked weakness and malaise. These symptoms persisted and were accompanied three days before admission by swelling of the eyelids. The other three who shared the same foods also developed similar symptoms, but their fate is not known.

*Examination.* The patient was a well developed and well nourished male appearing acutely ill. The face was flushed. There were periorbital edema of upper eyelids and slight photophobia. The pupils, sclerae, conjunctivae and retinae were normal. No superficial lymph nodes were palpable. The lungs and heart were not remarkable. There was sinus tachycardia (120 per minute) with a blood pressure of 130 systolic and 80 diastolic. The liver edge was palpable one finger below the costal margin, and it was not tender. The spleen was not palpable. No significant tenderness of the skeletal muscles could be elicited. His temperature was 103°F.

*Laboratory data.* Blood: hemoglobin, 95 per cent; white blood cells, 25,000, with polymorphonuclear leukocytes 45 per cent, metamyelocytes and band forms, 15 per cent, lymphocytes, 2 per cent, monocytes, 2 per cent, plasma cells, 1 per cent, and eosinophilic leucocytes, 35 per cent. Urine was negative. No ova or parasites were found in the stool. Cerebrospinal fluid was negative. Blood culture was negative. Electrocardiograms showed sinus tachycardia and changes suggestive of myocardial involvement. Blood chemical studies of liver and kidney functions were normal. Skin tests with *Trichinella spiralis* antigen in dilution of 1:500 were strongly positive and with dilution of 1:10,000 were faintly positive.

*Course.* On the third hospital day the patient developed tenderness of the skeletal muscles and occasional auricular premature contractions which were not present on admission. He continued to run remittent fever varying from 100° to 105°F., and leucocytosis persisted with eosinophilia as high as 22 per cent. His condition declined steadily and he died on the tenth hospital day.

*Necropsy findings. General, summarized.* Acute trichinosis; confluent bronchopneumonia of right and left lower lobes; congestion of all lobes of the lungs; fatty degeneration of liver; acute interstitial myocarditis; arteriosclerosis, mild, of coronary arteries without narrowing; partial atrophy of partly descended right testicle; cerebral congestion, mild; sarcosporidiosis with *Sarcosporidium* in the myocardium.

Only the microscopic findings in the skeletal muscles and the gross and microscopic changes in the heart will be described in detail.

*Skeletal muscles.* All the skeletal muscles were invaded by a great number of larvae of *Trichinella spiralis*. The muscle fibers inhabited by the larvae were swollen and could be recognized only as thin, pink, nucleated shells surrounding the larvae. In some areas no part of the muscle fiber was recognizable. The surrounding tissue was densely infiltrated by mononuclear cells, lymphocytes, plasma cells and polymorphonuclear leukocytes. The mononuclear cells contained small vacuoles. Many of the muscle fibers had lost their cross-striations. The larvae were in an early stage of encystment. They were coiled up and surrounded by a pale, basophilic, hyaline membrane containing a few large nuclei. The blood vessels were congested. None of the sections disclosed Sarcosporidia.

*Heart. Gross.* The heart weighed 230 Gm. It was of normal shape. The pericardial sac contained a moderate amount of serous fluid. The pericardial surfaces were smooth and glistening. The right auricle showed no gross abnormality. The tricuspid valve was normal. The right ventricle was of average size and thickness with a smooth and glistening endocardium. The pulmonic valvular cusps were thin and translucent. The pulmonary artery showed no gross changes. The left auricle appeared normal. The mitral valvular leaflets were thin and translucent and had a few yellow opaque areas at the base. There was slight thickening along the margin of closure. The chordae tendineae were thin, delicate and inserted in web-like fashion into the edge of the leaflets. The left ventricle was of normal size and thickness. The endocardium was thin, smooth and glistening. In the outflow tract there were a few subendocardial petechiae. The myocardium was less firm than usual and had a brown-red color. The aortic valvular cusps showed no gross changes. The coronary ostia were normal. The coronary arteries showed slight arteriosclerosis with no narrowing. There was an accessory right coronary artery. The aorta was elastic and had a few yellow intimal plaques.

*Microscopic observations.* All sections showed many foci of myocarditis. These consisted of infiltration between the muscle fibers of lymphocytes, some plasma cells and a few eosinophils. Many muscle fibers were fragmented and swollen. In these areas the cross-striations were indistinct. In some areas there was slight perivascular exudation of lymphocytes and a few eosinophils, without degenerative changes of the muscle fibers. The vessels were congested. No *Trichinella* larvae were seen. There were several small subendocardial and interfascicular hemorrhages in the myocardium of the left ventricle.

A section from the posterior wall of the left ventricle revealed a swollen muscle fiber, cut in cross section, which contained an oval cyst (fig. 1). The cyst was completely surrounded by a thin rim of sarcoplasm, and the nucleus of the muscle fiber lying adjacent to the cyst was normal. The cyst measured  $28.5\ \mu$  in its longest diameter. There was a faint external membrane,  $3\ \mu$  in thickness, and no radial striation or lamination could be made out. Within the cyst there were numerous spherical and oval bodies with a distinct, dark blue staining nuclear portion. No septa or central hyaline area were demonstrable. There were no inflammatory cells at the site, and the adjacent muscle fibers were normal.

Other sections of the heart failed to reveal the presence of sarcocysts.

*Case 2. History.* (Adm. #568074, P.M. #10648). The patient was a woman, aged 34 years, a native of Puerto Rico, who came to this country several years ago. She often ate in a small restaurant where she frequently had a native dish made up of pigs' ears, tails and tripe, lightly cooked and well seasoned. She was in good health until ten days before admission, when, shortly after a lunch of this preparation, she developed epigastric distress, and then diarrhea which persisted for seven or eight days. Three days before admission she began to have general aching and soreness of the body, fever, frontal headaches and pain on movements of the eyes. At this time she noticed that her face and eyelids were swollen.

*Examination.* The patient was a well developed and well nourished woman appearing acutely ill, with swollen eyelids and slight chemosis. Her pharynx was diffusely injected. The superficial lymph nodes were not palpable. The lungs and heart were not remarkable. The blood pressure was 100 systolic and 60 diastolic. There was sinus tachycardia (110 per minute). The liver and spleen could not be felt. There was tenderness of the eyelids



and of the muscles of the extremities and abdominal wall. Nuchal rigidity was present. The temperature was 101°F.

*Laboratory findings.* Hemoglobin, 85 per cent. Red blood cells, 4,490,000. White blood cells, 6,250. Differential: polymorphonuclear cells, 37 per cent; metamyelocytes and band forms, 38 per cent; lymphocytes, 11 per cent; monocytes, 2 per cent; eosinophiles, 12 per cent. Urine: trace to one plus albumin. Stools: no ova or parasites seen. Lumbar puncture: normal dynamics; cerebrospinal fluid contained 30 red blood cells per cu. mm. (probably a traumatic tap), Pandy test, negative, glucose, 20 mg., NaCl, 693 mg., and protein, 25 mg. per 100 cc. Blood urea nitrogen, 24 mg. per 100 cc. Blood glucose, 75 mg., total serum cholesterol, 140 mg. and cholesterol esters, 100 mg. per 100 cc. Carbon dioxide combining power 53 vol. per cent. Total plasma protein, 6.8 Gm., albumin, 4.6 Gm. and globulin 2.2 Gm. per 100 cc. Blood NaCl, 507 mg. per 100 cc. Throat cultures yielded *N. catarrhalis*, *Staph. albus* and *Strep. viridans*. Blood cultures were negative. Electrocardiograms showed no abnormality. Precipitin test for trichinosis was positive in antigen dilution of 1:1280.

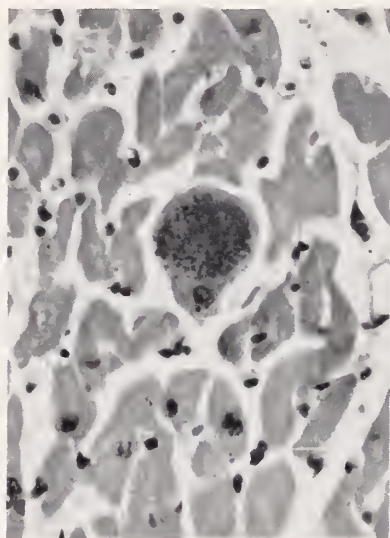


FIGURE 1

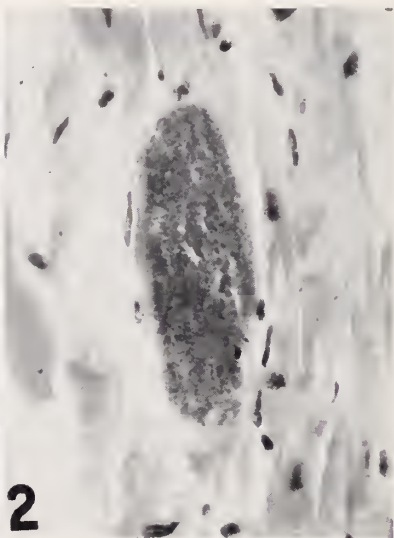


FIGURE 2

*Course.* The patient continued to run a high remittent fever and complained of severe muscular pain. On the third hospital day there developed persistent leucocytosis with eosinophilia varying from 12 to 2 per cent, the latter just a few days before death. On the tenth hospital day a biopsy of the deltoid muscle was performed. Microscopic examination of fragments of fresh muscle tissue crushed between two slides revealed many live and moving larvae of *Trichinella spiralis*. The patient's condition declined progressively; she lapsed into coma and died on the thirteenth hospital day.

*Necropsy findings. General, gross.* Acute trichinosis; acute interstitial myocarditis; pericardial effusion (60 cc. of clear, straw colored fluid); right hydrothorax; bilateral congestion and edema of lungs; primary tuberculous focus, right upper lobe; fibrous pleuritis, left lower lobe; fatty degeneration of liver; acute erosions of esophagus and stomach; endometrial polyp; cerebral edema; sarcosporidiosis with *Sarcosporidia* in the myocardium.

*Skeletal muscles.* All skeletal muscles were invaded by many larvae of *Trichinella spiralis*. (At the time of autopsy fresh muscle fragments squeezed between two slides and examined microscopically revealed many motile larvae.) The muscle fiber at the site of

inhabitation of the larva was markedly swollen and basophilic, with loss of cross-striations. Lying within the degenerating muscle fiber around the larva were multinucleated giant cells. There was diffuse and severe interstitial inflammation, not only around the site of larva inhabitation, but elsewhere. Many of the muscle fibers were fragmented and swollen, with hyaline degeneration and complete loss of cross-striations; and some of these fibers were infiltrated by inflammatory cells. The inflammatory cells were mononuclear cells, lymphocytes, plasma cells, some polymorphonuclear cells and eosinophiles, and a few multinucleated foreign body giant cells.

*Heart. Gross.* The heart weighed 220 Gm. It was normal in shape but slightly less than normal in size. The right ventricle was flabby and the left ventricle was contracted and firm. The pericardial sac contained 60 cc. of clear, straw-colored fluid. The pericardial surfaces were smooth and glistening. There were subepicardial petechiae diffusely scattered over the surface of the heart, especially over the right auricle and ventricle. Some of these petechiae had a dark red center surrounded by a bright red periphery. The right auricle was normal in size and had a smooth and glistening endocardium with many subendocardial petechiae. The auricular appendage was free from thrombus and the foramen ovale was closed. The tricuspid valvular leaflets appeared grossly normal except for a single hemorrhagic spot measuring 4 mm. in diameter near the base of the anterior leaflet. Chordae tendineae were not remarkable. The right ventricle was slightly dilated, and there were many petechiae visible under the smooth and glistening endocardium. The pulmonic valvular cusps were thin and delicate. The pulmonary artery was normal. The left auricle, mitral valvular leaflets and chordae tendineae showed no gross abnormality. The left ventricle was not enlarged and presented a glistening and smooth endocardium with occasional subendocardial petechiae. The aortic valvular cusps were grossly normal. The wall of the right ventricle measured 4 mm. in thickness and the wall of the left ventricle 12 mm. Cut surfaces of the myocardium were uniformly reddish brown, and there were a few tiny red streaks in the myocardium of the left ventricle. The coronary ostia and vessels showed no gross abnormality.

*Microscopic observations.* There were interstitial edema and scattered foci of interstitial infiltration by mononuclear cells, lymphocytes, plasma cells, few polymorphonuclear cells and few eosinophiles. Some of the muscle fibers were swollen without loss of cross striations. There were scattered foci of interstitial and subendocardial hemorrhage. No larvae of *Trichinella spiralis* were seen.

A section from the posterior wall of the left ventricle revealed a solitary cyst within a swollen muscle fiber. The cyst was elongated and measured  $108.5\ \mu$  in length and  $33\ \mu$  in width (fig. 2). It was completely enclosed by a thin rim of sarcoplasm which showed cross striation. No external membrane could be made out. The cyst was composed of numerous spherical bodies, each with dark blue staining nuclear portion. No septa or central hyaline area were demonstrable. The involved muscle fiber and adjacent ones did not show any degenerative change. There was no inflammatory reaction at the site or in the neighborhood of the cyst.

A section from another part of the posterior wall of the left ventricle showed a single cyst within a cross section of a muscle fiber which was swollen to three times the size of adjacent muscle fibers. Covering one pole of the cyst was a thin layer of sarcoplasm. The cyst was elongated and measured  $61.5\ \mu$  by  $30\ \mu$ . A thin, homogeneous external membrane,  $1.5\ \mu$  in thickness, was present, and it did not show radial striation or lamination. Within the cyst there were numerous spherical bodies with no particular arrangement into groups. No septa were demonstrable. There was a dark staining nuclear portion within each body. The adjacent muscle fibers were normal, and there was no inflammatory reaction in this area.

#### DISCUSSION

In both cases the sarcocysts were of the immature type first described by Darling (2, 7). The sarcocysts in the myocardium in cases of Manifold (9),

Lambert (10) and Gilmore, Kean and Posey (15) were likewise of the immature variety. In Hewitt's case (14) the sarcocysts infesting the myocardium were of the more mature type with septa dividing the cysts into compartments. In our cases, as in all the reported cases, the parasites were found within the individual muscle fibers with no inflammatory reaction around them.

It is of interest that the two cases described here were in patients who died of trichinosis, a disease which is transmitted to man by way of the gastrointestinal tract.

Very little is known about the life cycle of *Sarcosporidia*, and the mode of transmission to man is unknown. In view of the fact that the disease can be transmitted to some animals by feeding them foods contaminated with sarcocysts (4, 16), it is possible that the disease in man occurs by way of the gastrointestinal tract.

#### SUMMARY

Sarcosporidiosis in two fatal cases of trichinosis has been presented. The *Sarcosporidia* were in the myocardium in both cases, and they were incidental findings during microscopic examination of sections of the heart. The parasites were not observed elsewhere.

Of the eleven reported cases generally accepted as being authentic, four involved the myocardium. Our two cases possess certain features which are in common with these reported cases. The sarcocysts were of the immature type, they were found within individual muscle fibers, and there was no inflammatory reaction around the parasites or degenerative changes of the adjacent muscle fibers.

The two cases described herein are singular in that the disease occurred in association with trichinosis. The coexistence of the two diseases has not been previously reported.

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# PHRENIC NERVE PARALYSIS ASSOCIATED WITH ERB'S PALSY IN THE NEWBORN

## A CLINICAL AND ANATOMICOPATHOLOGIC STUDY\*

LOUIS B. TURNER, M.D. AND ALVIN A. BAKST, M.D.

The association of Erb's palsy with phrenic nerve paralysis is seen only occasionally in the newborn infant. Approximately 35 cases of this condition have been reported in the literature to date. Among these there have been 7 deaths, of which 5 were autopsied; in none was there recorded a dissection of cervical nerve roots. Because of this and the general lack of pathologic reports dealing with such material, a complete anatomico-pathologic study of a case is presented.

### CASE REPORT

*History.* (Adm. #578046) A white male infant, aged 6 weeks, was admitted to The Mount Sinai Hospital on March 17, 1948, because of progressively severe cyanosis, rapid respiration, and feeding difficulty since birth. He was a firstborn, delivered at term after a protracted labor lasting 21 hours. Breech presentation necessitated the application of forceps to the aftercoming head. He weighed 2.1 Kg. at birth, and required resuscitation. Shortly after delivery flaccid paralysis of the right arm was noted; the fingers and wrist seemed to move slightly. The infant had respiratory difficulty which interfered with feeding. This was intermittent at first, but later became continuous and increased in severity.

*Examination.* The child was poorly nourished, critically ill and markedly cyanotic. The respiratory rate was 80 per minute, with deep subcostal retraction on the right side with each inspiration. The heart and the mediastinum were found to be shifted to the left. This, as well as the paradoxical motion and elevation of the right leaf of the diaphragm, associated with inspiratory shift of the mediastinum farther to the left, was verified by fluoroscopy and by x-ray studies (fig. 1). The heart sounds were normal, with their maximum intensity in the anterior axillary line. Erb's palsy was noted on the right side.

*Course.* It was felt that the infant had an injury involving the phrenic nerve and upper portion of the brachial plexus on the right side, in all probability secondary to the trauma of birth. The child was given oxygen continuously from the time of admission to the time he expired, 44 days later. The respiratory rate varied, but was usually between 60 and 80 per minute. The Erb's palsy never showed any signs of improvement. Efforts to relieve respiratory distress by placing the infant on the right or left side, or propping him up, were of no avail. Penicillin was administered for prophylactic purposes and he remained afebrile throughout the clinical course. Feeding was always difficult because of respiratory embarrassment, a tendency to swallow air, and frequent vomiting. His 44th day in the hospital was marked by a sudden change, resulting in collapse. Aspiration of the mouth and oropharynx yielded no exudate or vomitus. The chest was dull to percussion everywhere and breath sounds were completely absent from the right chest. Many fine rales were heard over the entire left lung field. Total atelectasis of the right lung, with a diffuse pneumonitis of the left lung, was suspected. His condition declined rapidly and he died within a few hours after the onset of the collapse.

*Post mortem findings.* The body was that of a thin male infant weighing 3.2 Kg. There was slight atrophy of the right deltoid muscle but no other obvious muscle changes. The brachial plexus on the right side was exposed, dissected, and its nerve roots followed into

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\* From the Division of Pathology, Laboratories of The Mount Sinai Hospital, New York.

the spinal canal. The anterior roots of C5 and C6 were found avulsed at their junction with the cord (fig. 2). Branches of the brachial plexus, and both phrenic nerves were dissected

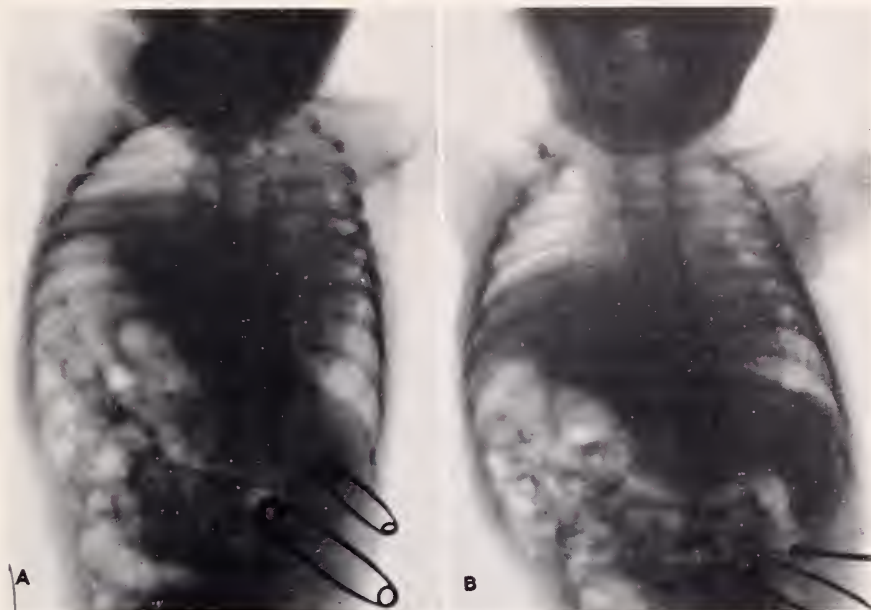


FIG. 1. Roentgenograms of the chest. A, left, taken in inspiration, and B, right, taken in expiration, showing marked elevation and paradoxical motion of the right leaf of the diaphragm, with shift of the mediastinum to the left on inspiration.

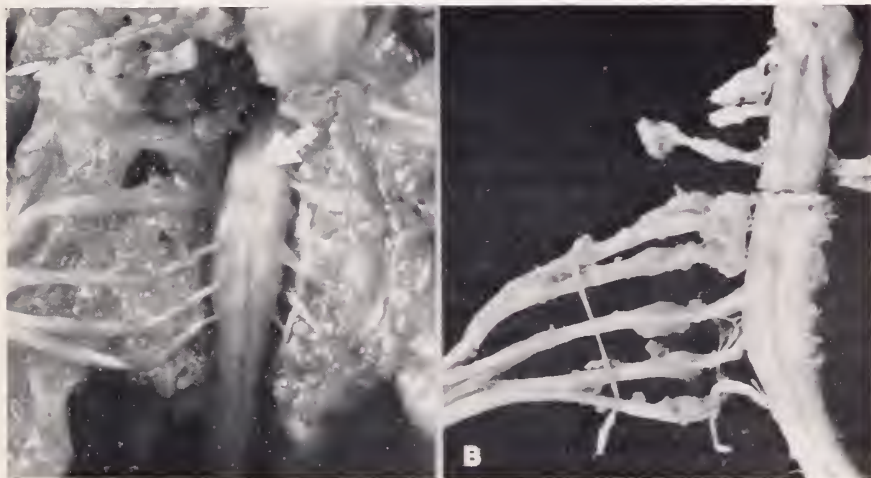


FIG. 2. Anterior aspect of the spinal cord and brachial plexus, showing the avulsion of roots C5 and C6 close to their origin from the cord.

A, left. Cord *in situ*, with the vertebral bodies removed.

B, right. Cord and plexus, dissected and removed from the spinal canal.

along their entire extent and were found to be grossly intact. The major portion of the right phrenic nerve apparently arose from C5, receiving a small twig from C4. The right

leaf of the diaphragm extended to the level of the second rib, the left to the fifth intercostal space. The left leaf of the diaphragm was normal, while the right leaf was markedly stretched and so thinned as to be translucent; it contained little muscle tissue.

The *lungs* weighed 50 Gm. together. The right lung was almost completely atelectatic, while the left revealed a few areas of atelectasis. There was no evidence of pneumonia, pulmonary edema or bronchitis.

The *heart* weighed 34 Gm. (normal 23 Gm.). The foramen ovale admitted a probe but was physiologically intact. There was slight, generalized myocardial hypertrophy.

The *liver* weighed 200 Gm. It presented a conical appearance, conforming to the shape of the elevated right diaphragm. It was otherwise normal.

*Microscopic observations.* *Nerves.* Paraffin sections of the phrenic, musculocutaneous, radial, and ulnar nerves stained with hematoxylin and eosin disclosed no significant altera-

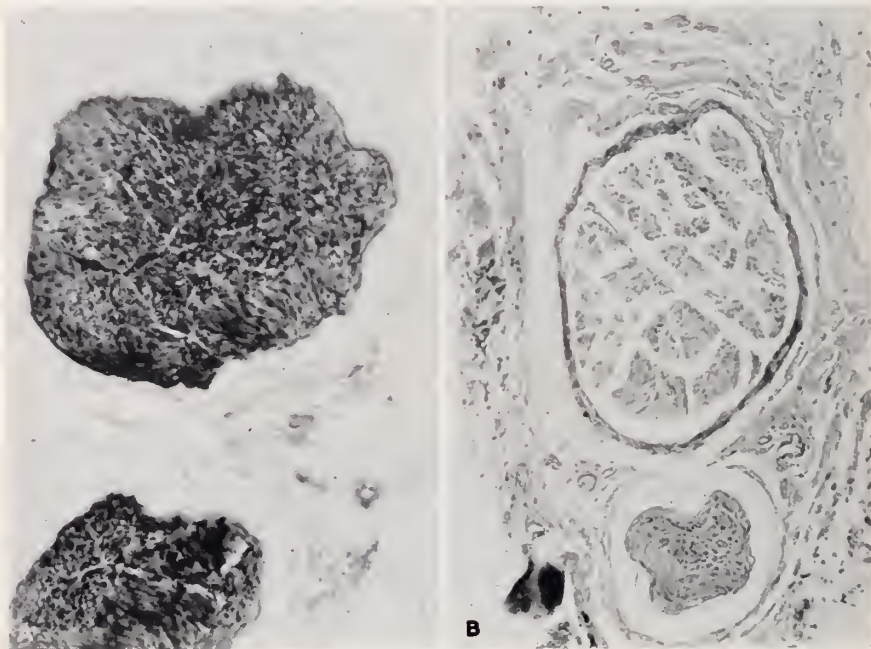


FIG. 3. A, left. Normally myelinated right ulnar nerve  
B, right. Demyelinated right phrenic nerve  
(Photomicrographs; Weil-Weigert myelin sheath stain)

tions. Frozen sections stained with Sudan IV showed no fatty changes or lipid droplets. Stains made on paraffin sections with the Weil-Weigert myelin sheath stain, however, revealed significant changes. The right phrenic nerve showed complete absence of stainable myelin. The musculocutaneous nerve was also almost completely devoid of myelin, but did contain a few, scattered, intact fibers. Sections of nerves arising from the lower roots revealed normally myelinated fibers (fig. 3).

*Spinal cord.* Celloidin sections of the cervical cord from C3 to C7 were studied with hematoxylin and eosin, Weil, and Nissl toluidine blue stains. No abnormalities were seen in sections taken from C3, C4 and C7. Sections taken from the region of C5 and C6 revealed an asymmetry of the cord due to shrinkage in size of the right anterior horn. This was accompanied by a great diminution in the number of anterior horn nerve cells; those that remained were shrunken, distorted in shape and revealed condensation of tigroid substance. There was a moderate glial proliferation on the right side. In addition, in both C5 and C6



on the right side there were small neuromas beneath the meningeal coverings, apparently attached to the anterior roots. These were probably traumatic in origin. The left side of the cord was entirely normal.

*Diaphragm.* The left leaf of the diaphragm showed normal musculature. Sections taken from corresponding areas in the right leaf of the diaphragm revealed most striking loss of muscle tissue, with hyaline changes and loss of striations in the remaining muscle fibers. There was a diffuse increase of interstitial fibrous tissue (fig. 4).

*Lungs.* The right showed marked diffuse atelectasis with areas of intra-alveolar hemorrhage; many mononuclear histiocytes were present in the alveoli. In the left lung there were focal areas of atelectasis interspersed among regions of normal aeration. The heart, liver, spleen, adrenals, pancreas, kidneys, thymus, and bones revealed no significant alterations.

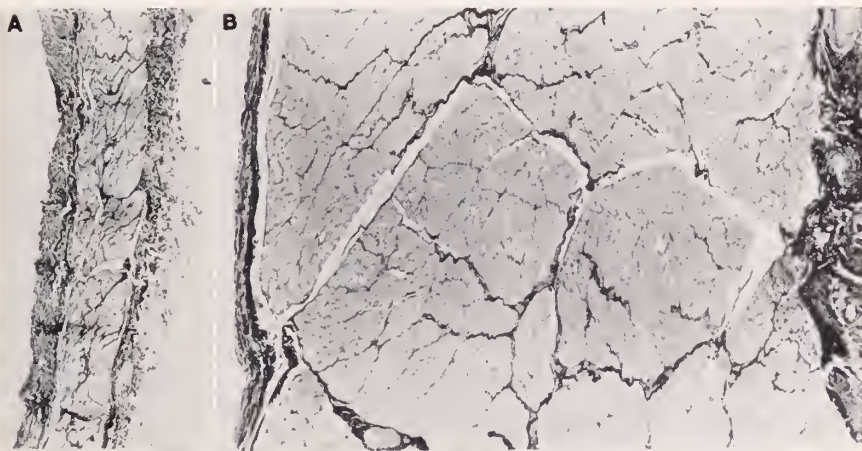


FIG. 4. A, left. Right leaf of the diaphragm, revealing marked atrophy of the musculature and interstitial fibrosis.

B, right. Left leaf of the diaphragm, showing intact structure.

(Photomicrographs, taken at same magnification; Van Gieson stain)

#### DISCUSSION

Clinically, our case is typical of those previously described. These infants are usually born after a difficult delivery, frequently from the breech position. They have an Erb's palsy associated with respiratory difficulty characterized by rapid, jerky respirations and cyanosis. The diagnosis can always be confirmed by fluoroscopy, which demonstrates paradoxical motion of the involved leaf of the diaphragm. Eighty per cent of the cases recover, some completely and within a few days; others take months to recover and may even then show residual diaphragmatic paralysis. Twenty per cent of the cases have proven fatal.

Landsberger (1) in 1926 was the first to describe an autopsy in a case of this sort. His patient, born from the breech position, was noted almost immediately to have a right-sided Erb's palsy and phrenic nerve paralysis, and died at the age of two months. At autopsy, he found atelectasis of the right middle and lower lobes of the lung, elevation of an atrophic right leaf of the diaphragm as high as the third rib, and a dome-shaped liver. The brachial plexus showed no gross or microscopic changes.



Tyson and Bowman (2) described the autopsy findings in one of their 5 cases, an infant aged 2 months, born after a difficult forceps delivery, who developed a right-sided Erb's palsy. The onset of the respiratory symptoms was at the age of 4 weeks, at which time fluoroscopy demonstrated paradoxical movement of the right leaf of the diaphragm. At autopsy they found "congenital heart disease, defective interventricular septum, patent foramen ovale, infarction in the wall of the left ventricle and atelectasis of the right lower, and left lower lobes of the lungs." They attributed the death to the congenital heart disease and infarction rather than to the diaphragmatic palsy. There was no reference to nerve changes or to exploration of the brachial plexus.

Rupilius (3) in 1934 reported a case born from the breech position after version, with Erb's palsy on the right and recurrent episodes of respiratory difficulty from the first day of life. Diagnosis was made fluoroscopically in the 6th week of life and the infant died in the 13th week. At autopsy, no changes in the brachial plexus or phrenic nerve were visible grossly. Microscopic examination of these nerves was not described. He mentions that the right sternocleidomastoid muscle was small and fibrotic. There was no examination of the spinal cord or the nerve roots.

Cocchi (4) in 1937 reported 3 cases, one of which died at the age of 2 months with a right-sided Erb's palsy and diaphragmatic paralysis. Autopsy of the fatal case revealed atelectasis of the right lung, elevation of an atrophic right diaphragm, and a dome-shaped liver. The brachial plexus was not dissected. The phrenic nerve appeared somewhat thin. Microscopically, demyelination, fragmentation, and fatty changes in the right phrenic nerve were demonstrated. The right leaf of the diaphragm showed fibrosis, with alteration and diminution of muscle fibres and nuclei.

Blattner (5) in 1942 presented the case of a 6 months old infant, born at home after a short labor, with the onset of respiratory difficulty, due to right-sided diaphragmatic paralysis, at the age of 4 months. (This child was one of 7 reported cases in which diaphragmatic paralysis occurred in the absence of brachial plexus injury.) At autopsy, the right lobe of the liver was found to extend high into the thoracic cavity; the right diaphragm was relaxed and stretched over it. The right lung was partially atelectatic. The right phrenic nerve was dissected high into the neck but appeared grossly normal. Microscopic sections of the phrenic nerves where they passed over the pericardium revealed a more cellular trunk on the right, with marked increase in nuclei. Masson stain demonstrated a striking increase in the amount of blue staining fibrillary substance. Only a few orange stained nerve axones could be distinguished. Scharlach R stain on a frozen section of this abnormal nerve disclosed no fat droplets.

In the previously described cases no gross alteration of the involved nerves was noted, but in none was there any mention of exploration of the roots of the cervical nerves. The pathogenesis of this condition has been subject to a great deal of speculation. Some observers thought that the injury was intrauterine in origin, resulting possibly from compression of nerves between the acromial

end of clavicle, the inner surface of first rib and the transverse processes of fifth and sixth cervical vertebrae. Others suggested direct injury to the spinal cord. Most observers, however, feel that the injury occurs during birth, possibly from overstretching of the cervical nerves by overextension, twisting and torsion of the head and neck, or by direct pressure by fingers or forceps.

In our case, it is most likely, in view of the traumatic delivery, that the injury occurred during birth. Also, since the principal pathological finding was a complete avulsion of the anterior nerve roots of C5 and C6 within the protective covering of the spinal canal, it is evident that the traumatic episode was one of tension rather than pressure.

It cannot definitely be stated that the findings in our case epitomize all cases of Erb's palsy associated with phrenic nerve paralysis, since the majority of these cases have recovered and autopsy material is scant. The eventual course followed by these infants may depend to a great extent upon the type of trauma suffered. In those patients who recovered it is reasonable to assume that the trauma was less severe; the nerves may have undergone only tension or pressure, without wide separation of torn nerve ends, and therefore were capable of regeneration. In cases like ours, however, where complete avulsion of nerve roots has occurred, no regeneration is possible, and the chances for recovery are correspondingly poor.

#### SUMMARY

A fatal case of right-sided Erb's palsy associated with ipsilateral diaphragmatic paralysis occurring in a newborn infant has been presented. At autopsy it was found that avulsion of the anterior roots of C5 and C6 had occurred and that the right side of the diaphragm was atrophic and elevated. Microscopic studies revealed degenerative changes in the right phrenic nerve, those branches of the right brachial plexus derived from the lateral cord, and in the anterior horn of the spinal cord at corresponding levels on the right side. Previous pathological studies of this condition have been reviewed.

We would like to thank Dr. Joseph H. Globus and Dr. Paul Klemperer for their help in the preparation of this report.

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## HEMATOMA OF THE RECTUS ABDOMINIS MUSCLE SIMULATING GYNECOLOGICAL DISEASE<sup>1</sup>

ROBERT I. WALTER, M.D., AND ROBERT LANDESMAN, M.D.

Idiopathic or non traumatic hemorrhage into the rectus abdominis sheath is uncommon though not rare. It occurs more frequently in women than in men and is most often mistakenly diagnosed as an ovarian tumor. The diagnosis is not difficult but is rarely made, probably because it is seldom considered in the differential diagnosis. A recent case on the Gynecological Service together with one admitted in 1942 prompted the present report.

### CASE REPORT

*Case 1. History* (Adm. #494612). This patient was a white woman, aged 59 years, gravida 5 para 1, 10 years post menopausal. Her chief complaint was pain in the right lower quadrant, 8 hours in duration. Ten days prior to admission she had had an upper respiratory infection accompanied by cough, diaphoresis and a chill. There was no history of trauma or blood dyscrasia. The pain in the right lower quadrant as discovered on questioning the patient post-operatively began following a paroxysm of cough.

*Examination* revealed a sub-acutely ill, obese woman complaining of pain in the right lower quadrant associated with a dry hacking cough. The temperature was 100.2°F. and the blood pressure 130 systolic and 80 diastolic. Moderate dyspnea was present and medium cracking rales were audible in both lung bases posteriorly. The abdomen, on palpation, revealed a moderately tender fixed ovoid mass 10 cm. in diameter, in the right lower quadrant and a localized muscle spasm. The lower pole of the mass could not be felt on pelvic examination. The cervix and uterus were atrophic and in a normal position. The left adnexa were normal.

The laboratory findings were hemoglobin, 10 gms.; white blood cells, 8850, with a normal differential count; sedimentation rate 22 mm. in 1 hour; urine normal; and blood Wassermann test, negative.

*Course.* The preoperative diagnosis was infarcted ovarian cyst with torsion of the pedicle or tumor of the cecum and broncho pneumonia. Penicillin and sulfadiazine therapy was begun and 48 hours after admission a right paramedian incision was made in the abdomen preparatory to exploration of the pelvis. The external rectus sheath was bulging and showed a dark purplish discoloration. When the sheath was incised several ounces of blood escaped. The right rectus muscle was friable and necrotic from its insertion to its origin and could not be separated from the blood and clots present. Where the superior epigastric vessels anastomosed with the inferior epigastric vessels in the region of the umbilicus, free bleeding was encountered which was easily controlled with mattress sutures. The entire right rectus was removed following suture ligation of its tendinous insertion in the pubic bone. The abdomen was not explored and the abdominal wound was closed in layers with cigarette drains placed within the rectus sheath at the upper and lower angles of the wound.

The drains were removed at the end of 5 days and antibiotics were continued for the same length of time. The wound closed by primary union and the post-operative course was uneventful. Histologic study of the excised muscle revealed extensive hemorrhage with beginning of focal organization.

*Case 2. History* (Adm. #494612). This patient was a white woman, aged 48 years, gravida 11, para 11, whose chief complaint was severe pain in the left lower quadrant. This pain was sudden in onset and had occurred for the first time shortly before admission.

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<sup>1</sup> From the Gynecological Service Mount Sinai Hospital.

There was no history of trauma, cough or severe exertion. Her past history revealed infrequent bouts of bilateral pelvic discomfort for many years. The menstrual cycle was normal.

*Examination* revealed an acutely ill patient. The blood pressure was 130 systolic and 80 diastolic. The temperature was 99.6°F. A tender, cystic, round mass approximately 12 cm. in diameter was palpable abdominally. Pelvic examination showed an uninfamed, parous introitus with a normal uterus. Several observers felt a tender poorly defined mass in the region of the left adnexa which they interpreted as an infarcted tubo-ovarian cyst or abscess.

The laboratory findings were hemoglobin, 90 per cent; white blood cells, 7500, with a normal differential count. The sedimentation rate was normal. Blood studies (bleeding time, clotting time and tourniquet tests) revealed no evidence of a blood dyscrasia.

*Course.* The abdomen was entered through a left paramedian incision and a large hematoma in the lower portion of the left rectus sheath was found. The clots were removed and hemostasis secured. The surgical note did not indicate which vessels were bleeding. In this case the peritoneal cavity was entered and explored. The findings were negative. The abdomen was closed in layers, sulfanilamide powder was placed into the rectus sheath and the latter was drained. The post-operative course was uneventful. The abdominal wound healed by primary union and the patient was discharged 13 days post-operatively.

#### DISCUSSION

According to Leske (1) who reviewed 100 case reports of hematoma in the rectus sheath, in 53 instances the etiology was undetermined. The syndrome occurs more frequently in elderly patients and is often antedated by a paroxysm of coughing. The diagnosis was correctly made in only 17 per cent of the cases. The most common incorrect diagnosis of ovarian tumor was made in 22 per cent of the cases. In these instances where the anatomical site was correctly diagnosed the lesion was confused with abdominal wall disease such as neoplasm, dermoid, hernia and granulomatous lesions. Ecchymosis of the abdominal wall was a late sign and rarely of aid in diagnosis. Signs of peritoneal irritation may occur due to absence of the posterior rectus sheath below the semi-lunar fold of Douglas and large accumulation of blood will distend or tear the visceral peritoneum in this region. In the presence of fever, leucocytosis, nausea and vomiting which may occur it is readily understood how the syndrome has been confused with appendicitis, incarcerated hernia and intestinal obstruction. Where the hemorrhage is large, signs of shock occur. A 4 per cent mortality occurred in the above series.

Torpin reviewed 27 cases of hematoma in the rectus sheath occurring in pregnancy with a mortality of 15 per cent and stated "This lesion should assume its rightful place as a dangerous hemorrhagic catastrophe of the 3rd trimester." It is difficult to agree with Torpin (2) who advises conservative treatment for this syndrome; i.e., blood transfusions, bed rest, ice bag and tight binder. It would appear more reasonable to treat the shock if present and stop bleeding surgically as soon as the diagnosis is made to prevent further extravasation of blood. With prophylactic use of antibiotics, drainage is probably not necessary.

#### CONCLUSION

1. Two instances of idiopathic hematoma of the rectus sheath, incorrectly diagnosed as ovarian tumors were reported.



2. The lesion frequently simulates intrapelvic pathology and should regularly be considered in the differential diagnosis, if the correct diagnosis is to be more frequently made.
3. A mortality varying from 4 to 15 per cent is reported in the literature.
4. The treatment advocated is early surgical intervention.

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# OSTEOGENESIS PRODUCED BY A CHEMICAL EXTRACT OF BONE<sup>1</sup>

JOEL HARTLEY, M.D., STANLEY S. TANZ, M.D., AND MONROE SCHNEIDER, M.D.

Osteogenesis is a complex and as yet incompletely understood phenomenon. The role of chemical substances in the differentiation of tissue into bone is particularly obscure, and reports of research aimed at isolating a substance capable of initiating osteogenesis have been few. In the experiment which we are reporting, new bone formation was observed after the injection of alcoholic extracts of post-fetal rabbit bone into the thigh muscles of rabbits. Other experiments, in which various fractions of the alcoholic extract were used, are being conducted and will serve as the subject of a subsequent report.

Ollier in 1867 demonstrated that boiled bone was not so effective for grafting as fresh autogenous bone. He assumed that this was caused by death of the cells in the boiled bone graft. Polletini, somewhat later, implanted one rabbit's ear cartilage into the subcutaneous tissue of another. New bone and cartilage were produced at a distance from the implant, and he inferred that there was a chemical substance in cartilage capable of stimulating bone and cartilage growth.

Bull implanted radial bone fragments of rabbits into their abdominal muscles. Where fresh bone was used, a cellular osteogenic tissue and bone formed around the transplant, but when boiled or heated bone was used, no bone formation took place. Thus, the bone transplants apparently contained some substance, destroyed or inactivated by heat, capable of stimulating osteogenesis.

Fischer in 1931 added embryonal cartilage to tissue cultures of fibroblasts and found that the fibrous tissue was transformed into cartilage. Speman, utilizing microsurgical methods with embryos, came to the conclusion that at certain decisive stages of development tissues became committed to a definite direction of growth. At these stages, certain regions of the growing organism acted as organization centers, and tissues transplanted into these regions developed in accordance with the growth direction of the center. When the center was transplanted to a new environment, the tissues maintained the direction of growth of their original site. This work suggested that chemical substances had a direct influence on the organization centers and could determine the direction of differentiation of nonspecific cells.

Levander attempted to isolate the postulated chemical substance. He injected alcoholic extracts of young rabbit bone into the thigh muscles of mature rabbits. New bone formation was present at the injection sites of 22 per cent of 70 animals. None of 80 controls, in which alcohol alone was injected, showed any new bone formation. Aqueous extracts of bone failed to provoke new bone formation in 10 other animals. Annersten, a pupil of Levander, and Bertelsen, pursued this work further. They confirmed the fact that the substance was not soluble in water and that an acid-alcohol extract of marrow gave the highest

<sup>1</sup> From the Orthopedic Service of R. K. Lippmann, M.D. and the Laboratories of The Mount Sinai Hospital, New York.

percentage of positive results, producing new bone in 8 out of 10 rabbits. Levan-der separated this substance from alcoholic solution with benzene. By saponi-fication, he divided the lipoid substances in the bone marrow into 1) an unsaponi-fiable fraction, 2) a fatty acid fraction, and 3) a residual solution after saponification and extraction of the first two. The osteogenic acitivity was very low in the unsaponifiable fraction, somewhat higher in the fatty acid fraction and completely inactive in the residue. He did not state the number of animals em-



FIG. 1. New bone formation in muscle at site of injection of alcoholic extract. New cartilage cells emanate from the mesenchymal tissue (A) which has replaced skeletal muscle. Transformation of cartilage (B) to bone (C). (Rabbit #6E, 53 days after first injection.)

ployed. LaCroix reported that in two instances, alcoholic extracts of the epiphyses of newborn rabbits caused new bone formation, when injected into the thigh of young rabbits.

No conclusive proof has been produced to demonstrate that the production of new bone at the site of injection into muscles is a specific phenomenon. In 1933 Von Severi obtained this reaction (in 5 animals out of 15) using 10 per cent quinine hydrochloride.

*Experiment.* Young rabbits, 4 to 5 weeks old, were sacrificed and the ends of the long bones were removed. Extracts of this material were prepared with 95 per cent alcohol, and allowed to stand at room temperature. After 24, 72 and 120 hours, the supernatant fluid in 3 cc. quantities was removed and injected into the thigh muscles of mature rabbits. The same volume of 95 per cent alcohol was injected into the opposite thigh as a control at the same intervals.

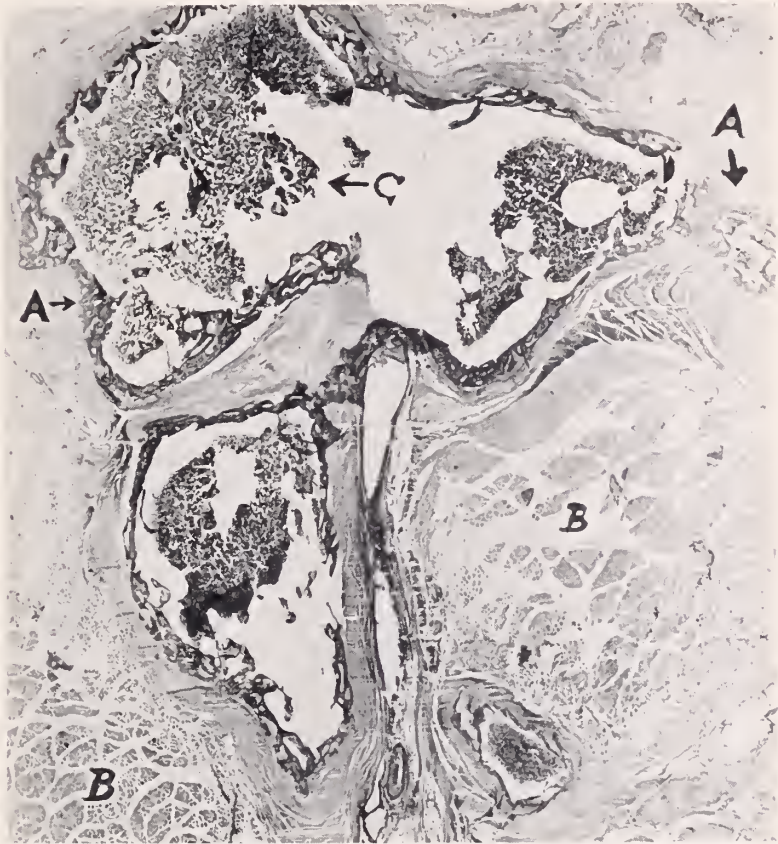


FIG. 2. Cancellous bone (A) imbedded in muscle (B). Marrow is present (C). (Rabbit #695E, 53 days after first injection.)

*Results.* In 3 of the 11 rabbits injected with the alcoholic bone extract gross and microscopic examination showed new bone formation. Necrosis of skeletal muscle and a mesenchymal reaction were seen at the control locations, but no bone formation occurred. These rabbits were sacrificed 53 days after the first injection. Although the series is small, the relative proportion is similar to that reported by Levander. Figure 1 shows an osseous nidus, with new cartilage cells, emanating from the mesenchymal tissue, which has replaced skeletal muscle. The gradual transformation from cartilage to new bone is apparent, with an osteoblastic reaction, cancellous bone and no osteoclasia. Figure 2 shows cancellous bone containing marrow, imbedded in surrounding muscle. Figure 3 shows new cancellous bone formation, with rows of osteoblasts lining the new osseous tissue. Marrow is present.

*Discussion.* The foregoing observations provide evidence suggesting that alcoholic extracts of the marrow and bone of rabbits contain a chemical sub-



stance or substances capable of stimulating bone formation when injected into skeletal muscle. Injections of alcohol alone do not produce this change. Experiments on various chemical fractions are now in progress in an attempt to isolate this osteogenic substance and to determine whether or not the substance is species specific.



FIG. 3. New cancellous bone formation (A). Rows of osteoblasts can be plainly seen (B). The tissue in the center of the bony trabeculae is marrow (C). (Rabbit #10E, 53 days after first injection.)

*Conclusions.* Experiments are recorded which confirm previous reports that alcoholic extracts of the growing ends of post-fetal bone contain a chemical substance which, when injected into muscle, can initiate new bone formation.

The authors wish to extend their grateful acknowledgment to Drs. Paul Klemperer and Sadao Otani for their help in reviewing the slides and to Miss Sarah Spector for her technical aid in preparing them.

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## ABSTRACTS

### AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out patient department of the Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Behavior and Psychologic Problems of Young Diabetic Patients. A Ten to Twenty Year Survey.*

H. DOLGER AND A. E. FISCHER. Arch. Int. Med., 78: 711, December, 1946.

The problems which arose in 43 young diabetic patients from childhood through adolescence to maturity are analyzed. No patient who had not been observed for at least ten years is included in this report. The type of home, its economic security and the contacts at school and in social life, all have especial influence on the reaction of the diabetic child to his disease. Specific problems of childhood became less disturbing with the onset of maturity. During adolescence, problems relating to vocation and marriage appear. Maturity usually brings about improvement in behavior, with the desire for independence being its outstanding characteristic. Marriage for the young diabetic person is difficult especially for the young women. The specific effects of diabetes on behavior are found to be unrelated to the age of onset, the duration or the severity of the disease. Diabetic regimentation, while necessary at first, produces behavior difficulties. The immediate and the more remote or cumulative effects of hypoglycemia on the brain are considered to be potentially serious. The results of intelligence tests are not significantly different from those of tests given to a similar socioeconomic nondiabetic group. The patients with better home environment have higher intelligence quotients and make more satisfactory adjustments to diabetes. Diabetes mellitus produces many psychologic problems which may result in abnormal behavior throughout childhood, adolescence and adult life.

*Combined Abdominothoracic Approach for Carcinoma of Cardia and Lower Esophagus.* J.

GARLOCK. Surg., Gynec. & Obst., 83: 737, December, 1946.

The author reports a new incision for exposure of the left upper abdomen and lower mediastinum. It was originally devised for resections of the lower esophagus and upper stomach for carcinoma. However, it is equally applicable for total gastrectomy, resections of the pancreatic body and tail, difficult splenectomy and retro-peritoneal tumors in this region.

*The Present Status of the Problem of Regional Ileitis.* J. GARLOCK. Am. J. Surg., 72: 875, December, 1946.

In this article, the author brings to date the present views on the surgical therapy of regional ileitis. On the basis of almost 200 cases, the conclusion is reached that in the vast majority of instances, ileo-transverse colostomy with ileal exclusion is the operation of choice. The long term follow-up studies have shown the best results following this operation.

*The Insulin Test for the Presence of Intact Nerve Fibers after Vagal Operations for Peptic Ulcer.* F. HOLLANDER. Gastroenterol., 7: 607, December, 1946.

This report describes a physiological test for the presence of uncut vagus nerve fibers

following any operation designed to intercept all vagal stimuli to the stomach. The test is based on the production of a degree of hypoglycemia of 50 mg. 100 cc. or lower, by the intravenous injection of 15 units of insulin. Adequacy of the hypoglycemia *must* be proved by blood sugar determinations. Fractional gastric analysis is performed to determine whether the resulting vagal stimuli, set up centrally, evoke any gastric secretory response. The validity of this procedure is supported by evidence derived from studies on gastric pouch dogs and on patients. A positive response to the insulin test—i.e., a distinct rise in the curve for free acidity of the gastric aspirates, concurrent with an adequate hypoglycemia—indicates that there are some uncut gastric vagal fibers. The test does not indicate the proportion of such intact fibers. A negative response with an adequate hypoglycemia is suggestive but not necessarily conclusive proof that all the gastric vagal fibers have been interrupted. First, there may be either a permanent or a temporary anacidity; fractional analysis with an alcohol test-meal or histamine will clarify such a question. Second, in the presence of a gastroenterostomy or a subtotal gastric resection, intestinal regurgitation may neutralize the acid output and a true positive response may be masked. Only after exclusion of these possibilities can a negative response be interpreted to indicate the presence of no uncut vagal fibers.

*Sinus Therapy by the Use of Volatile Inhalants.* L. KLEINFELD. *Ann. Otol., Rhin. & Laryng.*, 55: 912, December, 1946.

In this article a device is described which by using nasal suction in conjunction with an inhaler (such as the Benzedrine inhaler, Tuamine inhaler or Vonedrine inhaler) permits the entrance of these volatile vapors into the sinus cavities, as well as the nasal cavity, thereby helping to increase the patency of the sinus ostia. This has proved useful in the treatment of sinus conditions, especially in the subacute stage.

*Localized Proximal Jejunitis.* A. S. LYONS AND J. H. GARLOCK. *Arch. Surg.*, 53: 702, December, 1946.

Inflammation of the small intestine localized in the jejunum is uncommon. Moreover, very few such cases have been treated surgically. The operation heretofore has consisted of resection of the diseased segment. In the present case report the upper limit of the jejunitis was at the duodeno-jejunal junction. A duodeno-jejunostomy without resection was performed, after transection of the jejunum distal to the lesion. The patient's symptoms have not recurred during the three years since operation. This is the first reported instance of successful treatment of localized jejunitis by short-circuiting procedure.

*Effect of Injury and Effort on the Normal and the Diseased Heart.* A. M. MASTER. *New York State J. Med.*, 46: 2634, December, 1946.

Effort, either routine or unusual, does not affect a normal heart permanently. There is no such entity as "athlete's heart." During strenuous, continued activity, the heart may enlarge relatively, but this increase will disappear with cessation of the exertion. The life span of athletes is as long as that of the average person. The heart or its blood vessels may be ruptured by trauma and its walls contused. Arrhythmias may appear. Acute coronary artery occlusion may conceivably result from a severe accident from which the heart muscle is bruised. It is essential to distinguish the different acute coronary artery diseases. Acute coronary insufficiency without acute occlusion is an entirely different entity from acute coronary artery occlusion. The former, whether it be a physiologic involvement of the heart muscle, like the simple attack of angina pectoris, or whether it be actual myocardial necrosis, commonly results from physical exertion, trauma, emotional strain, operative procedures, carbon monoxide poisoning, pulmonary infarcts, and pulmonary artery embolization.

*Right-sided Aorta with Atypical Coarctation Involving Only the Left Subclavian Artery. Hypertension.* CAPT. A. M. MASTER (MC), USNR. *Am. Heart J.*, 32: 778, December, 1946.



A case is described of right-sided aorta with coarctation of the left subclavian artery. The diagnosis is made clinically and by ordinary x-ray film and then confirmed by angiocardiographic films. A small or absent left radial pulse in the presence of a hypertension in the right arm and a normal expected blood pressure in the lower extremities should lead to the consideration of the diagnosis of a localized coarctation of the left subclavian artery. Such causes as cervical rib, anomalous course of the left radial artery, tumors, and aortic aneurysm must first be investigated. With a localized coarctation of the left subclavian artery, just as with the typical coarctation of the aorta, a hypertension is usually present. It is probably a reflex mechanism originating from the nerves in the aortic arch and producing an increased vascular tone in all the extremities.

*Skin Manifestations of Capillary Fragility, Their Diagnosis and Treatment.* S. M. PECK AND A. COPLEY. *New England State Med. J.*, 235: 900, December, 1946.

The subject is discussed under the following headings: Vascular Anatomy of the Skin with Special Reference to the Site of Capillary Reactions; the Methods of Testing Capillary Fragility; the Mechanisms of Capillary Fragility; the Clinical Manifestations of Capillary Fragility as part of General Diseases and as purely Dermatological Conditions; the Relation of Capillary Fragility Tests to Clinical Diagnosis and Treatment. A thorough discussion of the vascular anatomy of the skin with special reference to the site of capillary reactions is given. Under the heading of 'Methods of Testing Capillary Fragility' the authors describe the known methods and compare the data which can be gleaned by the use of these methods. Apparently, no exact method is available for the evaluation of capillary resistance. There is discussed the suction or negative pressure test introduced by Hecht; the "capillary resistometer" of Da Silva-Mello and the Rumpel-Leede test as well as the puncture test, and the venom test of Peek, Rosenthal and Erf. The mechanism of capillary fragility is given in some detail. The clinical manifestations of capillary fragility are grouped under those due to general diseases such as drugs, toxins, endocrinological changes, etc. The pathogenesis of essential thrombocytopenic purpura is discussed. Under dermatological conditions which show capillary fragility are discussed such conditions as purpura due to drugs, Majocchi's disease, angioma serpiginosum, Schamberg's disease, Kaposi's disease, etc. The use of moccasin snake venom both in the diagnosis of capillary fragility and in the treatment of various disorders with capillary fragility is discussed.

*Colonic and Proctoscopic Diseases.* R. TURELL. *Surg., Gynec. & Obst.*, 83: 521, December, 1946.

In this article there are presented parts II and III of the review of the literature dealing with colonic and rectal diseases of which part I was presented in the November issue of the same journal. The following subjects are discussed: metabolic studies, continuous spinal anesthesia, skin bacteria, abdominal incisions, disruption of abdominal wounds, gas pains, postoperative ambulation, intravenous clotting (thromboembolism), poor risk patients, psychosomatic aspects, pilonidal disease, war wounds of the colon with comparative note on civil traumatic colonic wounds, traumatic perforation of colon, bleeding from rectum, digital examination, hemorrhoids, prolapse, fistula, incontinence, pruritus ani—plastic procedure, condylomata acuminata, cramp in rectum and backache in gastrointestinal disease.

*Effects of Barbiturates on Ocular Movements (Nystagmus).* M. B. BENDER. *Confinia Neurologica*, 7: 144, 1946.

Barbiturates, administered intravenously at a rate of 0.1 gm. per min. for 0.5 gm. produce coarse oscillating type of nystagmus when the eyes are deviated away from the midposition. These drugs also abolish opticomotor nystagmus induced by rotating stripe drum, all types of spontaneous congenital nystagmus, some types of pathological nystagmus and functional types of ocular palsies.

*Sensations of Electric Shock on Flexion of the Neck as a Sign of Head Injury.* M. B. BENDER AND L. T. FURLOW. *J. Neurosurg.*, 3: 212, 1946.

In a series of 17 cases of gunshot or shrapnel wounds and other types of injuries to the head, the patients complained of sensations of electric shock or paresthesiae in the extremities. These sensations were symmetrical, radiated along well known anatomical dermatomes, and could be elicited on flexion of the head. They appeared during the post-traumatic period (several weeks after the injury), changed from one set of dermatomes to another, and lasted for a short time (weeks to months). It is believed that the syndrome is caused by a simultaneous *contrecoup* injury to the spinal cord. The occurrence of such a syndrome after a head trauma should be considered as a significant sign of injury to the nervous system and should remove existing doubts as to the organicity of the case.

*The Management of Recurrent Pilonidal Disease.* E. GRANET AND D. PALMER. Tr. Am. Proct. Soc., 1946.

On the basis of reports in the recent literature and by the author's experience an expected recurrence rate of about 25 per cent for pilonidal disease treated by definitive surgical procedures in the Services is to be expected. Recurrent inflammatory disease in the form of sinuses, abscesses or both occurred after previous primary closure. Excluding immediate breakdown of the wounds due to hematomas or wound infection, late recurrences in many cases were probably due to insecure healing between the subcutaneous areolar (vascular) and posterior sacrococcygeal ligament (avascular). Breakdown of this suture line probably resulted in dead space; this subsequently became infected and eventually manifested itself in a deep sinus tract overlying the sacrum and coccyx. Recurrence following partial closure or open operations were less frequent in this series, (27 per cent). Failure of permanent healing in this group was most often due to failure of adequate drainage (a) mechanical factors (deep natal fold with large buttocks), (b) neglect of frequent and adequate postoperative wound toilet, (c) resumption of arduous duties with strain on fresh, friable, cicatrix at too early a postoperative period. Treatment of recurrent pilonidal disease is dependent on the type of lesion, *i.e.*, extent, depth of tract, fibrosis adjacent thereto, and age of the recurrent lesion. Few lend themselves to successful primary closure. Our safest procedure was exposure, saucerization and curettage of the base, a modified Buie marsupialization operation. Recalcitrant cases are common. In these, excision of the entire wound with plastic repair utilizing split skin grafts, or sliding grafts appears to be the most logical and practical solution.

*Device for Irrigation in Pericoronitis.* M. L. MORRIS. J. Am. Dent. A., 33: 1612, 1946.

A 20-gage luer-lok needle has been modified for proper irrigation of infected, partially erupted lower third molars. This, used as an adjunct to chemotherapy, hastens the subsidence of acute symptoms.

*Some Clinical Manifestations of Hypothalamic Dysfunction.* I. S. WECHSLER AND I. H. GROSS. *Confinia Neurol.*, 7: 89, 1946.

The authors report 3 cases with clinical manifestations of hypothalamic dysfunction. The first is that of a boy of 10 who, from the age of 2, had periodic attacks of vomiting, increase of blood pressure and lowering of temperature. In addition there was loss of weight, salivation, alteration of personality and vasomotor skin changes. Each attack was precipitated by some emotional upset and generally terminated spontaneously. The boy died suddenly in one of the attacks. The second case is that of a middle-aged woman who, following a fracture of the skull, developed grand and petit mal seizures. The latter, which occurred innumerable times a day, were characterized by pallor, acceleration of pulse rate and marked drop in blood pressure. They were completely and permanently controlled by ephedrine. The third case is that of a young woman who, in addition to grand mal epilepsy, also had petit mal attacks characterized by waxy pallor, rise in pulse rate and drop in blood pressure. Her attacks, too, were controlled though not cured by ephedrine. In both cases dilantin and phenobarbital favorably affected the major attacks but not the petit mals; whereas a stimulating drug had a sedative effect on the hypothalamic or autonomic type of petit mal seizures.



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